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

ABSTRACT & COMMENTARY

Comorbidities and Breast Cancer Survival: Lessons from the ATAC Trial

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

SYNOPSIS: In an analysis of a subset of breast cancer patients enrolled in the ATAC trial, it was apparent that age influences the risk of recurrence, and age and comorbidities significantly influence the risk of death without recurrence. The authors suggest assessment of comorbidities should be incorporated into decisions regarding adjuvant therapies.

SOURCE: Ring A, et al. Influence of comorbidities and age on risk of death without recurrence: A retrospective analysis of the arimidex, tamoxifen alone or in combination trial. *J Clin Oncol* 2011;29:4266-4272.

It is commonly understood that comorbidities complicate treatment for patients with cancer and negatively influence response rates and survival. Of course, some of these existing comorbidities could, in themselves, be life-threatening. By retrospectively analyzing results from the ATAC (Arimidex, Tamoxifen Alone or in Combination) study, Ring and colleagues examined the effects of comorbidities and age on treatment received, breast cancer-related mortality, and competing causes of mortality. ATAC was a double-blind randomized trial in which postmenopausal women with early-stage breast cancer were assigned to receive anastrozole, tamoxifen, or the combination.

This analysis examined 10-year median follow-up data in the two monotherapy arms (anastrozole, n = 3092; tamoxifen, n = 3094) of the ATAC study. Included in the protocol was an assessment of baseline comorbidities and comparison was made between women age < 70 years and women age ≥ 70 years. The cumulative incidence of breast cancer-related and non-breast cancer-related mortality was assessed according to age and comorbidities.

At enrollment, 1662 (27%) were age ≥ 70 years. This group of older women was more likely to

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undergo mastectomy and less likely to receive radiotherapy or chemotherapy. Women aged ≥ 70 years had an increased risk of recurrence compared with women aged < 70 years and a substantially increased risk of death without recurrence. The risk of death without recurrence increased with each increment in comorbidity score as determined by the Satariano comorbidity scale. The 10-year estimates for deaths without recurrence were 8.4%, 20.0%, and 30.4% for Satariano scores 0, 1, and 2, respectively ($P < 0.001$).

COMMENTARY

By examining the influence of comorbidities and age on the risk of death without recurrence in a population of older breast cancer patients enrolled in the ATAC study, it is apparent that for those older than 70 years, the risk of recurrence is greater, the risk of death without recurrence increases, and the risk of death also increases with comorbid conditions.[1] The authors conclude "formal assessment of comorbidities should be incorporated into decisions regarding adjuvant therapies." The risk of recurrence in those 70 years or older is not surprising because tumors were larger than in younger patients, fewer had lymph nodes examined, and they received less radiation therapy and chemotherapy. The authors recognize that these factors may contribute to the increased recurrence rate for the older population and add that there may be age-related differential compliance in the older population. Because these women were entered into a clinical trial, their state of health likely was superior at a comparable age to that of the general population of breast cancer patients. Does this report provide new information that will alter the approach to managing the elderly patient with breast cancer? The major strength of this analysis is a population with a consistent treatment intervention. Unfortunately, the information available to the authors is too shallow to dissect most of the factors and this limits their conclusions. Age is the most reliable dynamic considered in this analysis.

Retrospective reviews of comorbid conditions are likely to be incomplete and the commonly used systems rely primarily only on the number of reported comorbid conditions.[1] The reliability of reports of comorbidity depend first on their recognition and second on their documentation in the medical record. Most studies depend on extraction from medical records, while a prospective protocol-driven collection of comorbid conditions would be the ideal. The use of administrative datasets for the reconstruction of comorbidities usually results in under-reporting of some: e.g., alcoholism or mental disease. An earlier report of 1800 postmenopausal breast cancer patients diagnosed in 1992 with stage information demonstrated a higher mortality rate from breast cancer (51.3%).[2] This was likely the result of less of a consensus-driven standard of care for the older group. Comorbid conditions requiring active treatment deserve greater attention when assessing elderly breast cancer patients for treatment.

An earlier report of the ATAC trial noted that vasomotor and joint symptoms occurring in the first 3 months of therapy heralded a better endocrine response and fewer recurrences of breast cancer when compared with a group of women without these symptoms.[3] The authors conclude that this should be used to reassure the patients with symptoms of the importance of long-term adherence to the treatment regimen. They recognized the problem of continued compliance with a patient-managed oral treatment program. The decrease in recurrences may be a reflection of better patient compliance resulting in more symptoms of the treatment.

The efficacy of long-term adjuvant tamoxifen and aromatase inhibitors in breast cancer is reliant on patients conforming to recommendations of their physicians. A review of the published literature has shown that approximately one out of four patients prematurely discontinued therapy.[4] In breast cancer prevention trials, 20-46% of patients prematurely discontinued tamoxifen, and similar estimates have been made for compliance among patients treated in the private practice setting. Others have shown that even among those women with insurance, particularly the elderly, interruptions in adjuvant hormonal

therapy in the first year of therapy were common and often continued in subsequent years of therapy.[5] It is possible, or even likely, that decreased adherence to the treatment regimen for those age 70 years or older may explain their increased recurrence rate when compared with the younger study participants.

The author's conclusion that "formal assessment of comorbidities should be incorporated into decisions regarding adjuvant therapies" is credible and deserves attention. The assessment should also have some measure of severity and the need for treatment, because all comorbid conditions are not equal.[1]

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ABSTRACT & COMMENTARY

Gemcitabine Alone vs Gemcitabine Plus Radiotherapy in Patients with Locally Advanced Pancreatic Cancer: An Eastern Cooperative Oncology Group Trial

By Samir P. Kanani, MD

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

SYNOPSIS: In a muti-institutional prospective trial conducted from 2003-2005, 74 patients with unresectable pancreatic adenocarcinoma were randomly assigned to receive GEM alone (at 1,000 mg/m^2/wk for weeks 1-6, followed by 1 week rest, then for 3 of 4 weeks) or GEM (600 mg/m^2/wk for weeks 1-5, then 4 weeks later 1,000 mg/m^2/wk for 3 of 4 weeks) plus radiotherapy for a total of 50.4 Gy. Measurement of quality of life also was performed. Patients enrolled in Arm B (GEM plus radiation) had a higher incidence of grades 4 and 5 toxicities (41% vs 9%), but grades 3 and 4 toxicities combined were similar in both arms. No statistical difference was noted in quality of life. The primary endpoint of survival was improved with the addition of radiotherapy with 11.1 months for Arm B and 9.2 months for Arm A.

SOURCE: Loehrer P, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: An Eastern Cooperative Group Trial. *J Clin Oncol* 2011;29:4105-4112.

For patients with advanced pancreatic cancer, systemic therapy with radiotherapy has been the standard of care in the United States for decades, with median survival measured in months.[1] European trials have demonstrated no significant benefit to the addition of radiotherapy and 5FU to gemcitabine.[2] Numerous Phase 1 and Phase 2 trials have demonstrated the safety and efficacy of concurrent gemcitabine with radiotherapy. This intergroup trial was designed to test the hypothesis that concurrent radiotherapy and gemcitabine would improve survival and provide additional quality-of-life benefits when compared to gemcitabine alone.

Eligibility was limited to patients who were deemed surgically unresectable with an ECOG performance status of 0-2. The proposed sample size was 316 patients; however, the study was closed early because of poor accrual. The 74 enrolled patients were stratified according to performance status and weight loss and randomized to either gemcitabine or gemcitabine and radiotherapy. Patients were followed radiographically with CT scans, and quality of life was assessed using a validated FACT-hepatobiliary questionnaire.

Patients receiving combined GEM and radiotherapy experienced more grade 4 and 5 toxicity (41% vs 9%). Both arms had one grade 5 toxicity. Patients treated with GEM and radiotherapy experienced more problems with appetite and cramps, but

FACT-hepatobiliary analysis demonstrated no statistical differences. Median number of cycles delivered were 3 in both arms. Overall 30% of patients received all panned chemotherapy. Nearly 1 in 4 patients (24%) received less than 45 Gy of radiotherapy. Median progression-free survival was similar in both arms at 6 months. Overall survival was improved with the addition of radiotherapy from 9.2 months to 11.1 months (P = 0.017).

COMMENTARY

GEM is currently the most active single agent in pancreatic cancers. A number of trials have been conducted utilizing the radiosensitization of GEM concurrent with radiotherapy. Many of these trials used alternative fractionation of radiotherapy and smaller non-traditional radiotherapy fields because of the potent sensitizing power of GEM.[3] The current trial is the first trial utilizing a more "standard" radiotherapy portal and dose fractionation with GEM. It is also the first trial to show a survival advantage in a randomized fashion. The survival advantage comes with a price of increased grade 4 toxicity. In treating pancreatic cancers, the clinician must weigh the competing risks of local disease progression vs the risk of distant metastatic disease, thus weighing the importance of radiotherapy and chemotherapy. The authors conclude that radiotherapy concurrent with GEM is an important component in first-line therapy for managing unresectable pancreatic cancers. I would argue that a 41% risk of grade 4 and 5 toxicity is prohibitive in community practice, and caution should be used when trying to apply the results of this clinical trial. Treatment should be individualized for each clinical scenario. A patient with a small tumor deemed unresectable because of vascular encasement is certainly different than a patient with bulky pancreaticoduodenal adenopathy. Perhaps a combination approach of GEM alone combined with a hypofractionated course of radiotherapy with higher biologic equivalent dose directed at gross tumor could provide a tolerable balance between local control and distant metastatic control. Additional studies certainly are needed, as current standard therapy for advanced unresectable pancreatic cancer is palliative at best. Future directions will definitely involve testing novel chemotherapeutic agents in large populations. I believe that radiotherapy will play an important role in these studies as this trial points out.

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ABSTRACT & COMMENTARY

A Simple Tool For Predicting Chemotherapy Toxicity in Older Adults

By Gary Shapiro, MD

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

SYNOPSIS: This prospective multicenter study presents an 11-item model for predicting chemotherapy toxicity in older adults with cancer. Its stratification schema identified older adults at low (30%), intermediate (52%), or high (83%) risk for chemotherapy toxicity.

SOURCE: Hurria A, et al. Predicting chemotherapy toxicity in older adults with cancer: A prospective multicenter study. *J Clin Oncol* 2011;29:3457-3465.

The seven institution Cancer and Aging Research Group recruited 500 cancer patients (age 65 or older) who were about to receive a new chemotherapy regimen in an outpatient setting and had them complete a geriatric assessment before starting treatment. The patients had a mean age of 73, a variety of cancers (29% lung, 27% gastrointestinal, 17% gynecological, 11% breast, genitourinary 10%), and 61% had stage IV disease.

The assessment included functional status, comorbidity, medications, nutrition, psychological state, social support, and function. Most of these

domains were evaluated by validated patient self-reported measures, but there also was a short health care provider portion. Tumor characteristics, pretreatment laboratory data, and information regarding the chemotherapy regimen also were noted. The patients were monitored throughout their entire course of chemotherapy, and any chemotherapy-related toxicities were assessed and scored by two physicians using the Common Terminology Criteria for Adverse Events.

Grade 3-5 toxicity occurred in 53% (12% grade 4, 2% grade 5). The most common hematologic toxicities were leukopenia and anemia, and the most common non-hematologic toxicities were fatigue, infection, and dehydration.

Once the data were obtained, the authors used multivariate analysis to identify the risk factors associated with increased risk of grade 3-5 chemotherapy toxicity. The 11-item predictive model included the following risk factors: age ≥ 72 years; GI or GU cancer type; standard chemotherapy dosing; polychemotherapy; Hgb < 11 (male) < 10 (female); creatinine clearance < 34; hearing problems; ≥ 1 fall in last 6 months; requiring help taking medication; limited ability to walk 1 block; and decreased social activity.

COMMENTARY

Although older and younger patients derive similar benefit from chemotherapy, older cancer patients have a greater risk of toxicity. This is due to multiple factors that are not captured by existing predictors, like measurements of performance. Indeed, Karnofsky Performance Status was not correlated with chemotherapy toxicity in this study.

Hurria's predictive model has the advantage of simplicity. Five of its 11 questions (age, cancer type, hemoglobin, number and dosing of chemotherapy drugs) already are part of an oncologist's initial assessment. Though not part of every oncologist's routine, creatinine clearance is easily derived from existing data. The 5 "new" questions (hearing, falls, help with medicine, walking ability, social activity) are short and easy to ask. In addition to the ease with which it can be incorporated into a busy oncology practice, the model is readily adaptable as a simple electronic tool.

That is exactly what Martine Extermann has already done at Moffitt Cancer Center's Senior Adult Oncology Program.[1] Like Hurria, Extermann derived her model, which goes by the witty acronym CRASH (Chemotherapy Risk Assessment Scale for High-Age patients), from a multivariate analysis of variables obtained in a prospective study of the standard oncology pre-chemotherapy evaluation and a comprehensive geriatric assessment.[2] Her final analysis was based on 518 patients with a median age of 76. Sixty-four percent of the patients experienced severe toxicity (32% grade 4 hematologic toxicity and 56% grade 3-4 non-hematologic toxicity).

As in Hurria's model, all one needs to do to determine the risk of chemotherapy toxicity is add up the points assigned to each risk variable. Interestingly, the seven risk factors that came out in the multivariate analysis that determined the CRASH model are different from those that Hurria found to predict the risk of chemotherapy toxicity. The most important predictors of hematologic toxicity are diastolic blood pressure, instrumental activities of daily living (IADL), and lactate dehydrogenase (LDH); those for non-hematologic risk are performance status (ECOG), Mini Mental Status Exam (Folstein MMS), and Mini-Nutritional Assessment (MNA). Unlike the model developed by Hurria, CRASH incorporates chemotherapy regimen-specific risk data,[3] and this was found to be an important risk factor for both hematologic and non-hematologic toxicity.

Both the CRASH and Hurria models are influenced by the investigators' choice of screening tools: different data in gives different data out. For example, despite including regimen-specific risk data, the CRASH model did not include information regarding the dose of chemotherapy that actually was delivered, an important factor in older patients who often get reduced doses of chemotherapy. It is also interesting that cognitive function fell out of the multivariate analysis that produced the Hurria model. It is possible that cognitive issues were accounted for by measures (like social activity), but choice of cognitive assessment tools (MMS for CRASH and Blessed Memory Test for the Hurria model) may have been just as important.

Finally, it is worth noting that unlike the academic medical center consortium led by Hurria, patients for the CRASH model were also recruited from community cancer centers. Though internally validated, Hurria's model has yet to be validated externally and one wonders if it was influenced by the care that her patients received from teams with expertise in geriatric oncology. The CRASH model has the advantage of external validation, but, like the Hurria model, it needs to be studied in specific tumor types and stages.

While we wait for these models to be refined, busy oncologists have, at long last, two tools to help inform the decision-making process as they discuss chemotherapy with their older patients and their families.

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ILLUSTRATIVE CASE SERIES

Management of Multiple Myeloma in the Oldest Old

By Bindu Kanapuru, MD

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

An 88-year-old woman with history of hypertension, chronic kidney disease with baseline creatinine of 1.8 meq/dL, and osteoarthritis was seen in the emergency room for worsening pain in the right shoulder and fatigue over 2 weeks. Her son denied any recent illnesses, falls, changes in appetite, or change in urinary or bowel habits. He reported that his mother was able to perform her daily activities but has a sedentary lifestyle. Laboratory investigations in the emergency room revealed hemoglobin of 7.0 g/dL, calcium level of 12.0 mg/dL, total protein of 7.0 g/dL, albumin of 3.0 g/dL, and creatinine of 2.0 meq/dL. X-ray of the right shoulder revealed a lytic lesion in the upper end of the right humerus without apparent fracture. Also present was a serum M-spike of 3.5 g/dL with an associated immunofixation pattern consistent with an IgG lambda monoclonal protein. Quantitative IgG level was of 3460 mg/dL, whereas immunoglobulin A and immunoglobulin M (IgA; IgM) levels were both found to be 80 mg/dL (normal IgG, 640-1430 mg/dL; IgA normal, 70-300 mg/dL, normal IgM, 20-140 mg/dL). Serum lambda light chains were elevated to 2030 mg/dL, but kappa light chains were reduced. Beta-2 microglobulin was very high at 28.0 mg/L. A bone marrow biopsy showed infiltration with 65% plasma cells (some very dysplastic in appearance) consistent with a diagnosis of multiple myeloma.

How Should This 88-year-old Woman Be Treated for Her Multiple Myeloma?

Multiple myeloma is a malignant disorder of B cells characterized by proliferation of plasma cells in the bone marrow and is predominantly a disease of the elderly. The median patient age at diagnosis is 70 years. The incidence rates in those aged 50-54 is less than 10%; rates steadily increase with age and are greater than 35% in the elderly over 80 years of age.[1] The proportion of newly diagnosed patients over 80 years of age between 1950-1959 and 2000-2005 has grown dramatically and will likely continue to grow as the population ages. Over the past 2 decades, survival for myeloma has improved by 10% for patients aged 50-59 years and by 5% 60-69 years of age. However, there has been only a modest increase in survival in the 70-79 year old age group and no improvement in survival for those over 80 years of age. Older myeloma patients have less favorable features at presentation such as high International Staging System (ISS) and Durie-Salmon stage as well as other adverse features such as low hemoglobin and poor performance status.[2] Although these factors alone may account for the poor survival seen in the very old, it turns out that age alone has been found to be an independent risk factor for reduced survival by multivariate analysis. Whether this is related to increased toxicity from chemotherapy or inadequate therapy is unclear.

Clinical trials for myeloma have traditionally considered those over the age of 65 years to be "elderly," and protocols with representative numbers of typical octogenarians have been very few. Although chronological age should not be used to exclude patients from standard treatments, increased comorbidities and frailty in the oldest-old necessitate a modified approach. Melphalan and prednisone have been the standard therapy against which novel agents have been compared for the elderly patients. Current recommendation for those over 65 years old include Melphalan, prednisone, thalidomide (MPT); Bortezomib, melphalan, prednisone (VMP); and lenalidomide, dexamethasone (RD or Rd).

Meta-analyses of trials evaluating MPT vs MP have demonstrated a significant improvement in progression-free survival (PFS: MP 14.9 months and for MPT 20.3 months) and a trend toward benefit in overall survival. Most of the trials analyzed included participants younger than 75 years of age and with good performance status. In the Nordic trial which included > 20% of patients over 80 years of age and 30% of the participants with WHO performance status 3 or 4 the median PFS with MPT (10 months vs 6 months) was much shorter for those over 75 years of age than for those 65-75 years of age. No survival benefit to MPT over MP was observed and there was an increased risk of toxic deaths observed in those over 75 years of age.[4] Peripheral neuropathy and neutropenia were significantly increased in the MPT arm than MP in the IFM01/01 trial in which > 36% of patients were over 80 years of age, albeit with good performance status.[5] In the HOVON 49 trial, which enrolled more than 50% of the participants older than 75 years of age but less than 10% of the patients had PS of 3, a shorter EFS was observed in these patients without any survival benefit.[6]

The VISTA trial, which evaluated the benefit of adding bortezomib to Melphalan and prednisone in older patients, included 30% over 75 years of age and approximately 30% with Karnofsky performance status < 70%. The median time to progression was significantly improved (7.4 months) and median survival was not reached in those who received bortezomib. However, subgroup analysis showed that the significant benefit in survival was confined to those less than 75 years of age. In fact, 3-year overall survival (OS) in those older than 75 years age receiving MPT was 55.5%, which was similar to 3-year OS in all patients who received MP.[7]

Lenalidomide in combination with low- or high-dose dexamethasone was evaluated in a randomized trial that included > 50% of patients over 65 years of age. Although the low-dose dexamethasone regimen was associated with lower response rates, 1-year overall surviavl was significantly improved and treatment-related toxicity was significantly reduced. In the subgroup of patients over 70 years of age, the low-dose dexamethasone regimen did have relatively high response rates; however, PFS was slightly inferior compared to the overall population (25.3 months vs 22 months). Incidence of grade 3-4 hematological toxicity was 59% in the Rd group compared to 78% in the RD group. Firm evidence that these results can be applied to those over 80 years of age or those with poor performance status is lacking.

Based on the above discussion, the optimal management of the very elderly with myeloma remains to be defined. The novel drugs, although promising, have no definite survival benefit, have a less pronounced effect on PFS, and are associated with greater toxicity in the very old. Initiating treatment with Melphalan/prednisone is still a very reasonable therapy in these patients. Single-agent dexamethasone or prednisone are very active in multiple myeloma and should also be considered in frail elderly patients, especially acknowledging that treatment goals are directed at palliation with the least risk of toxicity. That stated, careful monitoring for side effects and dose modifications are essential to reduce the adverse effects from hyperglycemia, gastritis, edema, and bone loss. Different schedules of dexamethasone and prednisone are published and can be used based on the tolerance of the patient.[8,9]

Dose reductions or schedule modifications in the frail and very elderly may reduce toxicity without compromising efficacy. Weekly bortezomib with cautious dose adjustments for hematological and non-hematological toxicity may turn out to be an effective approach. The European Myeloma Network suggested stratifying patients for treatment based on age ≥ 75 years, frailty, comorbidity, disability, or presence of grade 3-4 non-hematological toxicities.[8] They recommended reduced dose treatment if even one or more of the above risk factors were present. Other authors have given recommendations on dose reductions in the very elderly or in poor performance status patients with starting dose of thalidomide at 50 mg or 100 mg, lenalidomide 10-15 mg. Again, these are recommendations derived more from anecdotal experience than randomized clinical trials, and without such evidence, clinical judgment is required.

Inasmuch as disease-directed treatments are untested in frail-elderly and are likely to have some associated toxicity and only modest efficacy, offering supportive care alone may be the best choice. Included would be appropriate management of infections, anemia, and palliative radiation for symptomatic bone lesions.

Case Continued

The patient was started on dexamethasone 20 mg daily for 4 days and this was to be repeated in 2 weeks. She received H2 receptor blockers for gastritis prophylaxis, packed red blood cell transfusions, intravenous fluids, and reduced dose bisphosphonates based on her creatinine clearance. An appointment was also made for palliative radiation to painful rib lytic lesions.

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CME Questions

1. By examining data from the ATAC trial, it is apparent that women over the age of 70 years:

a. were more likely to undergo mastectomy.
b. were less likely to receive chemotherapy or radiotherapy.
c. experience increased risk of breast cancer recurrence.
d. experience increased risk of death without breast cancer recurrence in accordance with increasing comorbidities.
e. All of the above

2. Which of the following comments regarding the treatment of pancreatic cancer combination therapy GEM and radiotherapy is *not* true?

a. GEM plus radiotherapy results in improved survival when compared to GEM alone.
b. The addition of radiotherapy to GEM increases grade 4 and 5 toxicity.
c. Median progression-free survival is improved with the addition of radiotherapy to GEM.
d. Health-related quality of life as measured by the FACT-hepatobiliary questionnaire was similar in patients receiving GEM alone as compared to patients receiving GEM plus radiotherapy.

3. Which of the following is *not* an important risk factor for chemotherapy toxicity in older adults with cancer?

a. Breast cancer diagnosis
b. Anemia
c. Social isolation
d. Limited walking ability

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]

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Barrett's Esophagus: What's the Risk?

Source: Hvid-Jensen F, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011;365:1375-1383.

FOR UNKNOWN REASONS, ADENOCARcinoma of the esophagus (E-ca) is experiencing the most rapid increase of any known cancer in the United States. Although the absolute incidence of E-ca pales next to lung, prostate, or breast cancer, the inexplicable proliferation of this cancer has spurred increased scrutiny of at-risk individuals. Barrett's esophagus, which is felt to represent an attempt at protective epithelial remodeling in response to the trauma of acid exposure, occurs in as many as 10% of individuals undergoing endoscopy for symptoms of GERD. Once Barrett's is identified, consensus group guidelines suggest ongoing surveillance, despite the absence of outcomes trials indicating that such surveillance improves survival.

The Danish Pathology Registry and Cancer Registry provide an opportunity to review data accrued for the entire population of Denmark. Follow-up of persons with Barrett's esophagus (n = 11,029) over a median of 5.2 years of observation identified 197 cases of E-ca, for an annual incidence of 0.12%. Likelihood of developing E-ca was increased in persons with higher degrees of dysplasia. Based on these data, the authors suggest that ongoing surveillance of Barrett's esophagus might wisely be limited to those with demonstrated dysplasia, since the incidence of E-ca in persons without dysplasia was so very low. ■

Life Expectancy: The Japanese Are #1

Source: Murray CJ. Why is Japanese life expectancy so high? *Lancet* 2011; 378:1124-1125.

EVEN THOUGH JAPAN SPENDS ESSENTIALLY half of what the United States spends on health care (8.5% of their gross domestic product vs 16.4% of ours), they have ranked No. 1 in life expectancy for 30 years. To what might we attribute their success?

That Japan provides universal health coverage can certainly be responsible for a portion of their favorable outcomes, but other factors are also at play. For instance, Japanese public health programs to reduce salt intake and become more aggressive about blood pressure control are credited with substantial reductions in stroke. Indeed, such Japanese hypertension programs have evoked a substantial decline in blood pressure among the population as a whole, especially in women (the gender in which successful blood pressure control is conspicuously less prominent in the United States).

Although it is difficult to measure the direct impact of one additional factor — educational attainment — on health, epidemiologic surveys do consistently indicate a linear relationship between education and positive health outcomes. The generally high educational attainment among Japanese may be a critically important factor.

Current health trends suggest that Japan may not stay in the No. 1 slot: Inadequate tobacco control and a rising BMI among the population, unless counteracted, may incur similar health decrements as have been seen in other nations. ■

The Calcium/Cardiovascular Disease Link

Source: Sabanayagam C, Shankar A. Serum calcium levels and hypertension among U.S. adults. *J Clin Hypertens* 2011;13:716-721.

THE RELATIONSHIP BETWEEN CALCIUM INtake — through diet and/or supplements — and vascular health is complex. Some recent epidemiologic surveys have found a positive association between calcium supplements and adverse cardiovascular (CV) outcomes, as well as vascular calcification (i.e., more CV disease and calcification with calcium supplementation than without). Because hypertension (HTN) is the most common vascular antecedent to adverse CV events, investigation of the relationship of calcium to blood pressure (BP) is pertinent.

The National Health and Nutrition Examination Survey (NHANES) has published cross-sectional data from diverse populations throughout the United States for more than 30 years. The authors obtained data from the NHANES population (n = 12,403) of adults over age 20 seeking to examine the relationship between serum calcium levels and BP.

Persons in the highest quartile of serum calcium were 1½ times more likely to have HTN than those in the lowest quartile. Even when adjusted for age, race, alcohol, body mass index, cholesterol, C-reactive protein, glomerular filtration rate, serum albumin, vitamin D,

and phosphorus, the relationship between calcium and BP remained.

Several mechanisms through which calcium might incur increased risk of HTN have been offered, including a direct vascular effect, parathyroid activity, and renal vasoconstriction. Before concluding that calcium is simply a "bad guy," it is important to recognize that several reports have shown that *dietary* calcium is *inversely* related to HTN. ■

What Factors Lead to Acquisition of *Clostridium difficile*?

Source: Loo VG, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *N Engl J Med* 2011;365:1693-1703.

The toxicity associated with intestinal habitation by *Clostridium difficile* ranges from asymptomatic colonization to life-threatening infection. In the United States, *C. difficile* is the most common cause of health care-associated diarrhea. Although the association of *C. difficile* with use of antibiotics and/or hospitalization is clear and well established, why certain individuals fall prey to infection/colonization — whereas most do not — remains ill-defined.

Loo et al performed a prospective study of patients admitted to Canadian hospitals over 15 months (n = 4143). Subsequent to hospital admission, *C. difficile* infection was identified in 2.8% (n = 117) and colonization in 3% (n = 123); excluded from these numbers were the 4.4% of individuals who were already *C. difficile* colonized upon admission.

As has been noted in previous observational studies, older age, antibiotic use, and use of proton pump inhibitors (PPI) or histamine-type 2-receptor antagonists (H2RA) were each associated with *C. difficile* colonization and infection. The mechanism by which PPI/H2RA use is associated with *C. difficile* remains speculative, but is attributed to disturbance of bacterial flora. Whether more restraint in use of antibiotics, PPI, or H2RA medications will reduce the incidence of serious *C. difficile* infections remains to be determined. ■

The Relationship Between Sleep and Hypertension

Source: Bansil P, et al. Associations between sleep disorders, sleep duration, quality of sleep, and hypertension: Results from the National Health and Nutrition Examination Survey, 2005 to 2008. *J Clin Hypertens* 2011;13:739-743.

It is probably obstructive sleep apnea (OSA) with which clinicians most familiarly associate hypertension (HTN). Indeed, some recent trials have found a remarkably high prevalence of previously unsuspected OSA in persons with resistant HTN. What about other sleep variances, such as persons with sleep movement disorders (e.g., restless legs, sleep apnea), short sleep (< 7 hrs/night), or poor sleep? The authors report on data obtained through the most recent National Health and Nutrition Examination Survey obtained through direct interview with 10,308 adults.

Overall, persons with HTN were statistically significantly more likely to have a sleep disorder than normotensive individuals (11% vs 6%). "Poor sleep" did not appear to be a relevant factor, but less than 7 hours of sleep nightly was. No gender or ethnicity differences were detected.

In contrast to prior data sets, this study did not find a consistent relationship specifically with sleep disorders and HTN. Rather, it was in persons who reported both a sleep disorder *and* short sleep that risk of HTN rose steeply: this combination was associated with more than a doubling of risk. Finally, the authors also note that more than two-thirds of persons with sleep problems had not discussed their issues with a health professional. ■

DPP4 Inhibitors are Associated with Reduced Risk of Hip Fracture

Source: Monami M, et al. Dipeptidyl peptidase-4 inhibitors and bone fractures: A meta-analysis of randomized clinical trials. *Diabetes Care* 2011;34:2474-2476.

In an era where concern about adverse consequences of pharmacotherapy on bone health are prominent — proton pump inhibitors associated with increased risk of hip fracture, bisphosphonates associated with an increased risk of spiral femoral fractures, and even thiazolidinediones noted to increase fracture risk — a more sanguine headline is certainly welcome.

The dipeptidyl peptidase-4 inhibitors (DPP-4) currently include three agents: sitagliptin, saxagliptin, and linagliptin, each of which provides a fairly similar degree of glucose reduction. The physiologic activity of GLP-1 (the primary pathway through which DPP-4 treatment enhances glucose control) includes activation of osteoblasts and inhibition of osteoclasts. Animal studies have shown that DPP-4 agents actually increase bone density, but no large, long-term clinical trial has confirmed a relationship between DPP-4 and fractures in humans.

Monami et al performed a meta-analysis on trials of DPP-4 inhibitors lasting 6 months or longer from which data on fractures was able to be extracted. Based on 28 trials of DPP-4 treatment (n = 11,880) vs comparator (n = 9175), the odds ratio for fracture was 40% less in persons receiving DPP-4 than in comparator. DPP-4 appear to have a protective effect on bone. ■

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Rivaroxaban Now Approved for Stroke Prevention

In this issue: New indication for rivaroxaban; new study on warfarin testing; medications causing adverse drug events; niacin as an add-on therapy; and FDA actions.

Rivaroxaban for atrial fibrillation patients

Rivaroxaban (Xarelto), Janssen Pharmaceutical's once-a-day oral Xa inhibitor, has been approved for reducing the risk of stroke in patients with atrial fibrillation. The drug was previously approved for prophylaxis of deep vein thrombosis in patients undergoing hip or knee replacement. Rivaroxaban is the second "non-warfarin" oral anticoagulant to be approved for this indication after the direct thrombin inhibitor dabigatran (Pradaxa). The approval was based on the ROCKET AF trial, a double-blind, randomized, noninferiority comparative trial with warfarin, which showed a rate of stroke or systemic embolism of 2.1% per year for rivaroxaban and 2.4% per year for warfarin. The study looked at 14,000 patients over 700 days of follow-up. Rates of major and non-major bleeding were the same with the two drugs, although the rate of intracranial hemorrhage was lower for rivaroxaban while the rate of GI bleeding was lower with warfarin. ROCKET AF showed noninferiority of rivaroxaban vs warfarin but not superiority (*N Engl J Med* 2011;365:883-891). The approval sets up a major marketing showdown between Janssen and Boehringer Ingelheim, the manufacturer of dabigatran, for this multibillion dollar market. Meanwhile, Pfizer and Bristol-Myers Squibb are jointly developing a third drug — apixaban, also a factor Xa inhibitor — which is undergoing an "accelerated review" by the FDA with approval likely in March 2012. All three drugs have the potential disadvantage of the lack of an antidote, a problem that seems to be plaguing dabigatran with more than 250 fatal bleeding episodes reported worldwide since the drug was approved in 2010. A recent report suggests that prothrombin complex concentrate may be an effective reversal agent for rivaroxaban but not dabigatran (*Circulation* 2011;124:1573-1579). ■

Warfarin testing every 12 weeks?

One of the major disadvantages of warfarin over the newer anticoagulants is the need for frequent prothrombin time monitoring and dose adjustment. Most guidelines recommend a maximum interval of 4 weeks between testing. A new study suggests that stable patients may be safely tested at 12-week intervals. A total of 226 patients who were on a stable dose of warfarin for at least 6 months were assigned to testing every 4 weeks, while the other half had blood tests done every 4 weeks, but sham INRs within the target range were reported for two of the three 4-week periods. The percentage of time in the therapeutic range was 74.1% in the 4-week group compared with 71.6% in the 12-week group (noninferiority $P = 0.020$ for a 7.5% point margin). Patients in the 12-week group had fewer dose changes and secondary outcomes, including major bleeding, thromboembolism, and death that were no different between the two groups. The authors conclude that assessment of warfarin dosing every

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12 weeks seems to be safe and noninferior to assessment every 4 weeks, although they recommend further study (*Ann Intern Med* 2011;155:653-659). This study is important given the marked cost differential between warfarin and dabigatran or rivaroxaban. Some patients, especially if they pay for their own medications, may opt to remain on warfarin if they are on a stable dose, especially if they only require testing four times a year. ■

Adverse drug events in the elderly

Although low cost, warfarin remains one of the most dangerous medications in common usage. In fact, hospitalizations for adverse events in the elderly are much more likely to be caused by commonly used medications, such as warfarin, rather than medications classified as high risk in the elderly, according to a new study from the CDC. Researchers used a national database of adverse drug events from 2007-2009 to estimate the frequency and rates of hospitalization after emergency department visits for adverse events in older adults to assess the risk of specific medications causing this hospitalization. It is estimated that adverse drug events led to nearly 100,000 hospitalizations during the 2-year period with nearly half among adults 80 years of age or older. Nearly two-thirds of the hospitalizations were due to unintentional overdoses. Four medications or medication classes were implicated alone or in combination in 67% of hospitalizations including warfarin (33.3%), insulins (13.9%), oral antiplatelet agents (13.3%), and oral hypoglycemic agents (10.7%). High-risk medications were implicated in only 1.2% of hospitalizations. The authors suggest that efforts to promote the safe management of antithrombotic and antidiabetic agents have the potential to substantially reduce harm to our older patients (*N Engl J Med* 2011;365:2002-2012). This study points out that we may be spending too much effort in managing "high-risk" medications in the elderly, while warfarin alone is responsible for a third of medication-related hospitalizations. ■

Is it time to retire niacin?

An editorial published online in the *New England Journal of Medicine* asks, "Niacin at 56 Years of Age — Time for an Early Retirement?" Retirement may be the logical next step after publication of the AIM-HIGH trial (see *Pharmacology Watch* July 2011), the National Heart Lung and Blood Institute's trial comparing niacin plus intensive statin therapy with intensive statin therapy alone in patients with established cardiovascular disease. The study was halted early when it was found that the addition of 1500-2000 mg of niacin per day to simvastatin, despite significantly raising HDL levels an average of 7 points, had no effect on the primary endpoint, which was a composite of the rate of death from coronary artery disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization (primary endpoint 16.4% niacin group, 16.2% placebo group; $P = 0.79$) (*N Engl J Med* published online November 15, 2011). The accompanying editorial suggests there is lack of evidence to support niacin as an add-on therapy in patients with cardiovascular disease who have well-controlled LDL cholesterol levels. Additionally, long-acting niacin is relatively expensive and frequently causes flushing — two additional factors that argue against continued use of the drug except, perhaps, in patients who are intolerant of statins (*N Engl J Med* published online November 15, 2011). ■

FDA actions

The news isn't much better for fenofibrate. The FDA has issued a safety communication for the cholesterol lowering medication stating that the drug may not lower the risk of major cardiovascular events based on data from the ACCORD Lipid trial. ACCORD (similar in design to AIM-HIGH) evaluated the efficacy and safety of fenofibrate plus simvastatin vs simvastatin alone in patients with type 2 diabetes. There was no significant difference in the risk of experiencing a major adverse cardiac event between the two groups, and women may have even experienced an increase in the risk for major adverse cardiac events with combination therapy vs simvastatin alone. The FDA is requiring the manufacturer of Trilipix brand fenofibric acid to conduct a clinical trial to evaluate the cardiovascular effects of the drug in patients at high risk for cardiovascular disease who are already taking statins (www.fda.gov/Drugs/DrugSafety/ucm278837.htm).

The FDA has approved a new formulation of zolpidem for treatment of insomnia in patients who wake up in the middle of the night and have difficulty returning to sleep. Zolpidem, originally marketed as Ambien and now available as a generic, is a short-acting hypnotic. The new product is a lower dose sublingual formulation that comes in a 1.75 mg dosage recommended for women and 3.5 mg for men. The lower dose for women is recommended because women clear the drug more slowly than men. It can be used if the patient has at least 4 hours of bedtime remaining. Zolpidem sublingual is marketed by Transcept Pharmaceuticals as Intermezzo. ■

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