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INSIDE

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Prostate Cancer with Bone Metastases at Presentation: Current Patterns of Care and Outcomes

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Using the CaPSURE registry, clinical features and prognostic factors were identified for the small percentage of patients who have bony metastases at the time of initial presentation. Although a protracted course (greater than five years) is expected, the presence of comorbidities and younger age were both found to have significant negative impact on survival.*

Source: Ryan CJ, et al. Initial treatment patterns and outcome of contemporary prostate cancer patients with bone metastases at initial presentation. Data from CaPSURE. *Cancer.* 2007;110:81-86.

Currently, the great majority of patients with prostate cancer are diagnosed with clinically localized disease. The unique features of those that present with bony metastatic disease are the subject of the report from Ryan and colleagues. The investigators examined the CaPSURE registry which is derived from the practices of 40 primarily community-based urologists across the country. The CaPSURE program[1, 2] does not include interventional trials and serves to describe community patterns of practice. Clinical data including laboratory results, pathology findings and treatments are provided by the participating physician. Additionally, information regarding comorbidities is collected by self-report questionnaire at the time of enrollment.

Of the 10,186 patients diagnosed and enrolled in CaPSURE between 1990 and 2003, 284 (2.4%) had bony metastases at the time of initial presentation, but data for seven of these were unavailable, resulting in a study population of 277 men. After a median follow-up of 3.8 years, 107 patients (39%) died. Of these, 68 (64%) died of cause related to prostate cancer. The 5-year survival of all patients

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was 71% and the median survival had not been reached at the time of last follow-up. Approximately 84% received some form of hormonal therapy. Prostate cancer-specific mortality was found to be correlated with the presence of comorbid illness, younger age at diagnosis, and a Gleason score of >7 in the primary tumor.

COMMENTARY

CaPSURE provides a unique data set from which community standards can be observed. The low incidence of bony metastases at the time of diagnosis (2.4%) reflects a general pattern of earlier diagnosis reported earlier.[3] Such may well be the result of increased public awareness and widespread utilization of prostate-specific antigen (PSA) testing. The great majority (85%) of men diagnosed with bony metastases at the time of initial presentation were treated with some form of androgen-deprivation therapy (LHRH agonist/antagonist or orchiectomy). Yet, it was surprising to see that 17% underwent some form of local therapy (eg, radical prostatectomy).

The analysis also revealed two findings of interest. The first relates to the influence of comorbidities, which increased both the rate of all-cause mortality as well as prostate-specific mortality. This is analogous to observations throughout the geriatric medicine literature on the influence of comorbidities on overall survival, but also to breast cancer in which the number of comorbidities directly relate to survival.[4,5] The other is the inverse correlation between age and risk of death due to prostate cancer. Again, the seeming paradox that younger patients who present with metastatic disease are more likely to have an aggressive course and succumb to their disease when compared to older patients with similar presentation is analogous to the situation with breast cancer in which younger patients are frequently found to have more aggressive disease.[6] Although, as the authors suggest, younger patients are more likely to die of the prostate cancer because there are less competing causes (ie, less comorbidities), there is now sufficient experimental data suggesting certain cancers exhibit less aggressive growth and spread in older hosts. Prostate cancer, hormonally-dependent like breast cancer, would seem to fit this category. ■

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Adjuvant Imatinib for GIST: Promising

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Imatinib mesylate has proven effective in the management of advanced gastrointestinal stromal tumors, but its use in the adjuvant setting is yet to be established. The current report details the experience from a single institution at which imatinib (400 orally/day) was administered for one year after radical surgery in patients considered at high-risk for recurrence. Compared to historical controls, recurrence rate was dramatically reduced. Confirmation of these findings await the results from ongoing randomized, prospective trials.*

Source: Nilsson B, et al. Adjuvant imatinib treatment improves recurrence-free survival in patients with high-risk gastrointestinal stromal tumors (GIST). *Br J Cancer.* 2007;96:1656-1658.

IMATINIB MESYLATE TREATMENT FOR PATIENTS WITH advanced gastrointestinal stromal cell tumors (GIST), particularly those with *KIT* exon 11 mutations has been demonstrated to provide excellent therapeutic value[1] in

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terms of remission rates and overall survival. However, its efficacy in the adjuvant setting has not been established. To address this, Nilsson and colleagues in Göteborg, Sweden reviewed their single institution experience.

Twenty-three consecutive patients (mean age, 56 years; range 21-82 years) diagnosed with high-risk GIST between February 2001 and June 2005 received imatinib mesylate (400 mg orally/day for one year) after radical tumor resection. Of the 23, 19 (83%) had tumors with mutations in *KIT* or PDGFRA (platelet-derived growth factor receptor α). The mean tumor size was 9.4 cm (range 2-35 cm) and the mean Ki67 max % (ie, maximum percentage of cells positive with Ki67 immunostains) was 7.0 (s.d., 5; range 2-10%). The mean follow-up after imatinib treatment was 40 months (range 18-62 months). For comparison, the clinical outcomes of 48 patients (mean age 67 years, range 25-87 years) detailed in a prior series of GIST[2,3], matched for "high-risk" features (tumor size, max % Ki67) were examined. In that series, patients were not treated in the adjuvant setting, but were followed carefully for the occurrence of recurrent disease. For this group of historical controls, the mean tumor size was 12.3 cm (range 3.5-33 cm) and mean Ki67 max % was 11.7 (s.d. 11.8, range 0.5-40%). These patients had a mean follow-up of 36 months (range 2-151 months). Of the 48, 30 (63%) had tumors with mutations in *KIT* or *PDGFRA*.

Only one of the 23 patients receiving adjuvant imatinib therapy developed recurrence, and this was 22 months after completing the one year of adjuvant therapy. In contrast 32 of the 48 patients (67%) in the control group developed recurrent disease.

COMMENTARY

These findings lend strong rationale to the use of imatinib in the setting of high risk, post resection GIST management. However, caution must be exercised in retrospective comparisons. The groups were not quite comparable (patients were somewhat older, with larger tumors and with fewer KIT mutations). Yet, one cannot help but be optimistic that these findings will be confirmed in prospective, controlled trials. In that regard, it is worthy of mention that several such trials are underway. One trial (ACOSOG Z9001) compares imatinib treatment (400 mg/day for one year) with placebo in patients with resected tumors ≥ 3cm. The EORTC (trial 62024) examines imatinib treatment (400 mg/day) vs placebo for intermediate and high-risk patients for a duration of two years, and SSG XVIII examines imatinib treatment (400 mg/day) for either one or three years in those with high risk.

The current retrospective analysis is the first in what is likely to be a series of publications on the value of imatinib for selected patients with intermediate or high-risk GIST. However, with the high response rate demonstrated in the palliative setting, it will take additional studies to determine whether the benefits of treatment in the adjuvant setting will translate to overall improved survival.

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Progression Risk for Smoldering Myeloma

ABSTRACT & COMMENTARY

By Andrew Artz, MD, MS

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

Synopsis: *Information on prognostic factors and progression rates from smoldering (ie, asymptomatic) myeloma to multiple myeloma and amyloidosis are limited. In this observational study from the Mayo Clinic database, the risk of progression was 73% at 15 years in 276 patients. In the first 5 years, the annual progression rate was 10% per year, 3% per year in the following 5 years, and only 1% per year thereafter. The progression risk was greatest in those having > 10% plasma cells at diagnosis. Smoldering myeloma frequently progresses, and the greatest risk occurs in the first 5 years after diagnosis.*

Source: Robert Kyle, et al. Clinical Course and Prognosis of Smoldering (Asymptomatic) Multiple Myeloma. *N. Eng. J. Med.* 2007. Vol 356:2582-2590.

MONOCLONAL GAMMOPATHIES ENCOMPASS A spectrum of disorders related to a clonal prolif-

eration of plasma cells. Although not necessarily distinct entities, diagnostic criteria separate monoclonal gammopathy of unknown significance, smoldering multiple myeloma, and multiple myeloma. To diagnose multiple myeloma (as opposed to smoldering), The International Working Group requires a monoclonal gammopathy (without defining a concentration), clonal bone marrow or plasma cells, and organ impairment (ie, hypercalcemia, renal insufficiency, anemia, lytic lesions of the bone, and/or bacterial infections).[1] Multiple myeloma absent organ manifestations has been termed smoldering multiple myeloma, usually categorized as ≥ 3 g/dL serum monoclonal or ≥ 10% marrow plasma cells without myeloma related signs or symptoms. The risk of progression and prognostic factors has not been well characterized.

Investigators at the Mayo Clinic retrospectively reviewed the institutional records for evidence of an IgA or IgG monoclonal gammopathy ≥ 3 g/dL and/or ≥ 10% or more plasma cells from 1970 to 1995. Active myeloma or amyloidosis or having received chemotherapy were exclusion criteria. The time to progression to active multiple myeloma (ie, anemia, hypercalcemia, renal insufficiency or bone lesions) or amyloidosis with either one requiring therapy was determined. Among 3549 patients diagnosed with myeloma, 276 (8%) met criteria for smoldering myeloma. The median age was 64 years and 62% were men. The serum monoclonal protein at diagnosis ranged from 0.5 to 5.4 g/dL and 52% had a concentration < 3 g/dL.

In the follow-up period, 85% of smoldering myeloma patients died. The probability of progression to amyloidosis or active myeloma was 51% at 5 years and 66% at 10 years, almost always to active myeloma (97%) rather then amyloidosis. Risk factors for progression in the unadjusted analysis included monoclonal protein concentration, IgA isotype (as opposed to IgG), presence of urinary light chain, > 20% bone marrow involvement by plasma cells, reciprocal reduction in other immunoglobulins, and pattern of marrow involvement. Serum monoclonal and plasma cell marrow involvement predicted progression in multivariate analysis. They constructed a scoring system to stratify progression risk. Thus, progression was 87% for those having ≥ 10% plasma cells and ≥ 3 g/dL monoclonal protein, 70% for those having ≥ 10% plasma cells and < 3 g/dL monoclonal protein, and 39% in the 27 patients having < 10% plasma cells but ≥ 3 g/dL monoclonal protein. Median time to progression was 2 years, 8 years, and 19 years, in the respective groups ($P < 0.001$).

COMMENTARY

Smoldering multiple myeloma may be defined as meeting criteria for multiple myeloma but absent symptoms. The authors report on the risk of progression to myeloma and amyloidosis from smoldering myeloma defined as > 3 g/dL monoclonal protein in the serum and/or > 10% bone marrow plasma cells but lacking anemia, renal insufficiency, skeletal lesions, or recurrent infections.

Defining risk can help determine monitoring strategies and allow appropriate patient counseling. While the progression rate of smoldering myeloma to active multiple myeloma or amyloidosis is high, variable definitions and study populations contribute to imprecise estimates. In one study, for those without progression after one year, the rate of evolution was reported to be 3.3% per year[2] and are considerably higher than that of monoclonal gammopathy of unknown significance.[3]

The authors suggest a time-dependent impact of disease progression such that the risk of progression is greatest within the 5 years of diagnosis at 10% per year, 3% per year for the following 3 years, and then approximately 1% annually. The data are instructive and confirm the high progression rate of smoldering myeloma.

Methodological limitations present a major obstacle to applying the data to clinical practice. The bias of this observational study is particularly problematic and not properly discussed. Patients were not prospectively or uniformly followed which impairs accurately determining progression rates. More problematic is not addressing the actual time of diagnosis. Patients may have been identified and/or referred because of recent symptoms (fatigue) or worsening laboratory findings (rising monoclonal gammopathy). Thus, they may have been diagnosed with MGUS of smoldering myeloma before and this could easily account for a high progression rate after the Mayo Clinic diagnosis. It would be very useful to know when the first diagnosis of a monoclonal protein was identified clinically. A population-based survey would be very helpful in this regard to better understand the biology and true progression rate of from smoldering myeloma. Referral bias may also hinder generalizability. Do these patients represent the routine patient in non-academic clinical practice?

The diagnostic criteria for smoldering myeloma, although standard, require comment. Diagnostic

thresholds are essential to establish prognosis, guide treatment, and enable comparisons across studies. The World Health Organization (WHO) criteria for active myeloma differ somewhat, incorporating plasma cell number and monoclonal protein concentration but not mandating symptoms. By WHO criteria, many patients may have met criteria for active myeloma.

The three prognostic groups created used plasma cells ≥ 10% and monoclonal protein ≥ 3 g/dL as cut points. The very small numbers (26/276) in the "best risk group" where bone marrow plasma cells were < 10% prevents precise estimates or conclusions. These risk groups should be validated in other studies. Established prognostic markers for myeloma were not available but could prove more useful in stratifying patients. For example, the International Staging System accurately stratifies active myeloma by serum albumin and beta-2 microglobulin.[4] FISH analysis, MRI and other modalities may better define risk groups although these are high-cost tests that may not be available everywhere.

To the extent the patients in this study represent those who oncologists see in clinical practice, the data are highly relevant. Patients presenting with smoldering myeloma to the oncologist probably do have a high progression rate in the first 5 years. This suggests focusing follow-up testing early in the disease course, especially for patients having > 10% marrow plasma cells. Alternatively, for those who have been followed for 5 years, a less aggressive monitoring strategy could be considered.

The therapeutic armamentarium for multiple myeloma continues to increase and suggests intriguing possibilities. Will treatment of smoldering myeloma prevent progression or prolong survival? Would early treatment lead to cures in some patients? Might bisphosphonates prevent progression of skeletal lesions? ■

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Prognostic Importance of Leukocytosis in P Vera

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a review of the Mayo Clinic experience over 50 years with polycythemia vera, the prognostic factors including leukocytosis were examined in the context of outcomes such as the development of leukemic or fibrotic transformation, thrombosis and overall survival. At the time of diagnosis, advanced age, a history of arterial thrombosis and leukocytosis were independent predictors of inferior survival. Leukocytosis during follow-up was also a predictor of leukemic transformation and venous thrombosis.*

Source: Gangat N, et al. *Br J Hematol.* 2007;138:354-358.

It is now understood that a JAK 2 mutation occurs in up to 90% of cases of polycythemia vera (PV).[1,2] Compared with the general population, survival is shorter for PV patients, primarily as a consequence of leukemic transformation, development of myelofibrosis, or vascular events.[3] Established guidelines target hematocrit of 45% or less in male and 42% or less in female patients.[4]

Recently, it has been observed that leukocyte counts of greater than 15 x 10^9/L in patients with polycythemia vera is associated with increased risk for myocardial infarction.[5] Leukocytosis is also known to heighten both arterial and venous thrombosis risk[6] and reduce survival[7] in patients with the related myeloproliferative disorder essential thrombocythemia (ET).

In the current report, Gangat and colleagues review the Mayo Clinic experience with polycythemia vera in the context of leukocytosis. The study population included a review of all records of patients with polycythemia vera at the Mayo Clinic between the years 1956 and 2005 for whom sufficient follow-up data was available through November 2006.

There were 459 study patients available with a median of 64 months (range 0 to 562 months). Among this group there were 146 (31.8%) deaths, 54 (11.8%) post-

polycythemia vera myelofibrosis (MF) and 34 (7.4%) leukemic transformations (LT) documented. By univariate analysis, overall survival was negatively associated with advanced age, a history of arterial thrombosis (either at diagnosis or during follow-up) or leukocytosis (using a cutoff level of either 10 x 10^9/L or 15 x 10^9/L [P = 0.008 and 0.002, respectively]). By multivariate analysis, age greater than 60 years leukocyte count greater than 15 x 10^9/L and arterial thrombosis at diagnosis retained their significance with regard to negative impact on overall survival. A risk stratification model based on leukocyte count of greater than 15,000 x 10^9/L and an age greater than 60 years generated three risk categories with a median survival of 272, 152, and 108 months in the absence of both risk factors or presence of either one or both risk factors respectively (P < 0.001; hazard ratio [HR] for high risk group = 5.57, 95% confidence interval [CI]: 3.45-9.02; HR for intermediate group = 2.18, 95% CI: 1.48 to 3.23).

Among several clinical and laboratory parameters evaluated for association with leukemic transformation, including specific drug exposure history, only leukocytosis was identified as an adverse prognostic factor (P = 0.001 for leukocyte count greater than 15 x 10^9/L and P = 0.006 or leukocyte count greater than 10 x 10^9/L).

COMMENTARY

These results are consistent with an evolving literature describing the prognostic importance of leukocytosis in both polycythemia vera and essential thrombocythemia.[6, 8-10] It now appears that an elevated white count in the context of myeloproliferative disorder portends a greater risk for leukemic transformation, venous thrombosis, possibly arterial thrombotic events and less favorable survival. Thus, it becomes a relevant question whether early and aggressive cytoreductive therapy in PV or ET patients with leukocytosis would favorably influence the adverse prognosis associated with the elevated white count. ■

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Managing Epidermal Growth Factor Receptor Inhibitor-Associated Skin Reactions

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Epidermal Growth Factor Receptor Inhibitors have proven to be effective cancer therapy for selected conditions, but skin toxicity is common. At an international multidisciplinary meeting with representation of medical oncologists, dermatologists, nurses and pharmacists, a set of guidelines were developed to assist in management and enhance the likelihood of uninterrupted therapy.*

Source: Lynch TJ, et al. *The Oncologist.* 2007;12:610-621.

Treatment with epidermal growth factor receptor inhibitors (EGFRIs) has been shown to improve survival in patients with several types of cancer, including lung, pancreatic, and colorectal cancers.[1,2] The drugs—including erlotinib (Tarceva), cetuximab (Erbitux), and panitumumab (Vectibix)—work by interfering with cell-signaling abnormalities that contribute to cancer development and growth. Unfortunately, the EGFRIs carry a substantial risk of skin reactions—more than half of treated patients have some type of skin toxicity, most commonly an acne-like rash.[3] Although the reactions most likely occur because the receptor blocked by the drugs also performs key functions in normal skin, the precise mechanism is incompletely understood. Immunohistochemical studies show treatment with EGFRIs leads to abolishment of phosphorylated EGFR in all epidermal cells and reduced expression of MAPK[4]. Inhibition of EGFR in basal keratinocytes leads to growth arrest and premature differentiation. This is demonstrated by upregulated expression of cyclin-dependent-kinase inhibitor p27, keratin-1, and signal transducer and activator of transcription-3 (STAT-3) in the basal layer; markers of differentiation that are normally only observed within the suprabasal layer.[4] These mediators result in attraction of leukocytes and other effectors of

inflammation. It is curious that patients who have received radiotherapy prior to EGFRI administration are often spared EGFRI dermatologic toxicity in the areas of skin that had received prior irradiation.[5] However, caution must be exerted in those receiving concurrent EGFRI and radiotherapy as the dermatologic reaction may be exacerbated by irradiation.

Thus, EGFRI skin toxicity is likely to be a direct consequence of the targeted therapy, and it is not surprising that some have associated anti-tumor efficacy with severity of skin reaction. This relationship has been most extensively reported with erlotinib, for which several trials have demonstrated a relationship between severity of the skin reaction and anti-tumor response.[6,7] For example, in a phase II study in which 57 patients with advanced non-small cell lung cancer (NSCLC) received erlotinib (50 mg/day), for those with no rash, median survival was 1.5 months. In contrast, patients with a grade 1 rash had a median survival of 8.5 months and patients with a grade 2-3 rash had a median survival of 19.6 months.[6, 7] A similar association was found for elotinib-treated head and neck and ovarian cancer patients[8] and for cetuximab treated patients with colorectal, head and neck, pancreatic and NSCLC patients.[9]

Accordingly, to maximize therapeutic potential, appropriate management strategies have been developed. In an effort to provide consensus recommendations, an international, interdisciplinary EGFRI dermatologic forum was convened in October, 2006. A brief summary of recommendations follows:

- All patients receiving EGFRIs should be advised to use a moisturizer and protect against exposure to sunlight—the rash may be more severe in sun-exposed areas.
- Reactions are classified as mild, moderate, or severe, based on the extent of rash, itching or other symptoms, and the risk of infection.
- Treatment is targeted to severity: mild steroids and/or antibiotics, stronger medications for moderate reactions.
- If the rash becomes severe, the guidelines call for reduction in the EGFRI dose, along with other medications. Treatment should be interrupted only if the reaction still hasn't cleared within two to four weeks. Once the rash has decreased, treatment with EGFRIs can be resumed—if the skin reaction returns, it will likely be manageable.

COMMENTARY

These recommendations (briefly summarized in the lefthand column below, but detailed completely in the manuscript) are those of an expert panel, but the authors clearly underscore the need for further studies to validate their approach. Until then, the expert guidelines seem both reasonable and well-founded. One theme that is emphasized throughout the report is that in the majority of cases, there is no clinical need to withdraw EGFRI treatment. Even with the most severe skin reactions, suspension of EGFRI treatment often needs only to be temporary, and resumption of treatment is possible.

Thus, this report presents a useful management algorithm for an increasingly common problem encountered by practicing oncologists. Although the consensus is derived from expert opinion and not primary evidence, the recommendations seem logical and practical; a good first start. Practitioners are encouraged to obtain a copy of the useful tables and diagrams within this paper. These provide useful management tips, which for now represent a reasonable and intelligent "standard" approach. ■

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CME Questions

32. Dermatologic toxicity with epidermal growth factor receptor inhibitor therapy occurs in approximately what percentage of patients?

a. 10%
b. 25%
c. 40%
d. >50%

33. Among prostate cancer patients who at the time of initial presentation are shown to have bone metastases, the median survival is:

a. less than 6 months
b. 18 months
c. 4.2 years
d. greater than 5 years

34. With regard to treatment of GIST with imatinib, Nilsson and colleagues from Sweden have demonstrated a benefit of treatment by which type of analysis:

a. retrospective, historical control
b. prospective, single arm trial
c. randomized, placebo-controlled trial
d. none of the above

35. What did Kyle and colleagues determine about smoldering (asymptomatic) multiple myeloma?

a. Thalidomide increases progression-free survival
b. Annual progression to active myeloma or amyloidosis was greater in the first 5 years than subsequent years
c. Progression to active myeloma was very uncommon
d. Interphase FISH predicted progression rates

36. An elevated white blood count at the time of diagnosis and during follow-up of patients with polycythemia vera was found to predict:

a. A higher risk of leukemic transformation
b. A higher risk of venous thrombosis
c. Less favorable survival
d. All of the above

Answers: 32 (d); 33 (d); 34 (a); 35 (b); 36 (d)

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Significance of Anemia in Small Cell Lung Cancer

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SSRIs Associated With Low Rate of Birth Defects, Studies Show

In this issue: *SSRIs are safer in pregnancy than previously thought; Estrogen therapy in younger women may be of benefit in preventing cardiovascular disease; Warfarin is substantially better than antiplatelet therapy in preventing stroke in patients with atrial fibrillation; The FDA tightens regulations regarding dietary supplements, Lyrica is approved for treatment of fibromyalgia.*

SSRIs are associated with a low rate of birth defects according to 2 new studies in the *New England Journal of Medicine*. SSRIs are often taken by women in their childbearing years, but the risk of birth defects has been unclear. Paroxetine (Paxil) specifically has been associated with omphalocele and heart defects, but there is little data on the risk of other SSRIs. In the first study from Boston University and Harvard, researchers assessed the association between first-trimester maternal use of SSRI and birth defects among nearly 10,000 infants with and over 5,800 infants without birth defects who participated in the Sloan Epidemiology Center Birth Defects Study. Use of SSRIs was not associated with significantly increased risk of craniosynostosis (odds ratio 0.8), omphalocele (odds ratio 1.4), or heart defects overall (odds ratio 1.2). Analysis of specific SSRIs and specific deficits showed significant associations between use of sertraline (Zoloft) and omphalocele (odds ratio 5.7) and septal defects (odds ratio 2.0) and between use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio 3.3). There were no significant associations with other defects with other SSRIs or non-SSRI antidepressants. In the other study, researchers from the CDC and University of British Columbia looked at data obtained on 9,622 infants with major birth defects and 4,092 control infants born between 1997 and 2002. Records were obtained from birth defects surveillance systems in 8 U.S. states and controls were selected randomly from the same geographic areas. Mothers were interviewed regarding exposure to potential risk factors including medications before and during pregnancy. No significant associations were found between maternal use of SSRIs overall during early pregnancy and congenital heart defects or most other categories or subcategories categories of birth defects. Maternal SSRI use was associated with amencephaly (odds ratio 2.4), craniosynostosis (odds ratio 2.5) and omphalocele (odds ratio 2.8). Their conclusion was that maternal use of SSRIs during early pregnancy was not associated with significantly increased risk of congenital heart defects or most other categories or birth defects. There was an association with SSRI use and 3 types of birth defects, but the absolute risk was small and further studies are warranted (*N Engl J Med* 2007; 356:2675- 2683, 2684-2692). An accompanying editorial points out that 2 previous stud-

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ies had suggested a relationship between paroxetine and cardiac malformations including ventricular septal defects, an association that was not found in these current studies. Although a small rate of congenital heart malformations, including right ventricular outflow tract lesions, were found the rate was still low, less than 1%. The editorialists, Dr. Michael Green from Massachusetts General states, "The 2 reports in this issue of the Journal, together with other available information, do suggest that any increased risks of these malformations in association with the use of SSRIs are likely to be small in terms of absolute risks." (*N Engl J Med* 2007; 356:2732-2733). ■

Estrogen for Younger Postmenopausal Women

Another follow-up study from the Women's Health Initiative suggests that estrogen therapy in younger postmenopausal women may be of benefit in preventing cardiovascular disease. Analysis was done on the "estrogen-only" wing of WHI in women who had undergone hysterectomy prior to enrolling in the study and were not treated with progesterone. Women age 50 to 59 were treated with 0.625 mg per day of conjugated equine estrogens or placebo. CT heart scanning was done at entry to the study and after a mean of 7.4 years of treatment and 1.3 years after the trial was completed. The endpoint of mean coronary-artery calcium scores was lower among women receiving estrogen (83.1) than those receiving placebo (123.1) (P = 0.02 by rank test). After adjusting for coronary risk factors, the odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared to placebo were respectively 0.78, 0.74, and 0.69. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P = 0.01), 0.55 (P < 0.001), and 0.46 (P = 0.001). For women who had calcium scores greater than 300 the multivariate odds ratio was 0.58 (P = 0.03) in an intention-to-treat analysis and 0.39 (P = 0.004) among women with at least 80% adherence. The authors conclude that in women age 50 to 59 years old at enrollment, estrogen treatment resulted in a lower calcified plaque burden in the coronary arteries compared to placebo. They also point out that estrogen has complex biological effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways (*N Engl J Med* 2007; 356:2591-2602). An accompanying editorial points out that not only did women in this analysis who were treated with estrogen have lower calcium scores, women in whom hormone replacement therapy was initiated at a younger age also had a 30% reduction in total mortality and did not have significant increases in any adverse outcomes examined. This supports the "timing hypothesis" for hormone replacement therapy that suggests that the cardiovascular benefits of hormone replacement are only evident if treatment is started before atherosclerosis develops. (*N Engl J Med* 2007;356:2639-2641). ■

Warfarin Better for Atrial Fibrillation Patients

Recent meta-analysis has confirmed the value of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation. Twenty-nine trials involving more than 28,000 patients were reviewed. Compared with control, warfarin and antiplatelet agents reduce stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%) respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy, and increases in extracranial hemorrhage assisted with warfarin were small. The authors conclude that warfarin is substantially more efficacious at preventing stroke in patients with a fibrillation than is antiplatelet therapy (by approximately 40%). (*Ann Int Med* 2007; 146: 857-867). ■

FDA Actions

The FDA has strengthened its regulations regarding dietary supplements, issuing a "final rule" requiring current good manufacturing practices for dietary supplements. The rule ensures the supplements are produced in a quality manner, do not contain contaminants or impurities, and are accurately labeled. Manufacturers will also be required to report all serious dietary supplement-related adverse events to the FDA by the end of the year.

Pregabalin (Lyrica-Pfizer) has been approved for the treatment of fibromyalgia, the first drug approved for this indication. Fibromyalgia, which is characterized by pain, fatigue, and sleep problems, affects up to 6 million people in United States. Approval was based on 2 double-blind, controlled trials involving 1,800 patients that showed improvement in pain symptoms at doses of 300 mg or 450 mg per day. The drug has already been approved for partial seizures, postherpetic neuralgia, and diabetic neuropathy. ■