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Cardiovascular Effects of Tamoxifen

ABSTRACT & COMMENTARY

Synopsis: *Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT) provide the unique opportunity to assess the cardiovascular effects of tamoxifen. One impetus for this investigation was the results of the HERS trial, a large, randomized study of postmenopausal women with cardiac disease that showed an early harmful effect with estrogen/progestin replacement therapy. If such a paradigm applied to tamoxifen, too, then deleterious effects on the heart might compromise the survival benefit from its protective effect in relation to breast cancer. Reis and colleagues published the results of their analysis of the NSABP data and reported a neutral impact on cardiovascular outcomes. They concluded that, when used for breast cancer prevention, tamoxifen is not associated with beneficial or adverse cardiovascular events.*

Source: Reis SE, et al. *J Natl Cancer Inst*. 2001;93:16-21.

During the years 1992 through 1997, the nsabp enrolled 13,388 women at risk for breast cancer into its Breast Cancer Prevention Trial. Included were women older than the age of 60, women 35-59 years old with a greater than 1.33% predicted risk of breast cancer over 5 years, and those women with a history of lobular carcinoma in situ (LCIS). Early results were reported in 1998 and did not reflect an influence by tamoxifen on cardiovascular risk.[1] Reis and colleagues recently published updated results of this randomized, placebo-controlled, double-blind study with a median follow-up of 57 months for 13,194 evaluable women.

Based on self-reported histories of myocardial infarctions and/or angina, the study participants were split into those reporting a cardiac history (n = 1048; 8%) and those without a history (n = 12,146; 92%). Women were then randomized to tamoxifen 20 mg q.d. or placebo. Seventy-six percent of the tamoxifen patients were compliant with the study therapy, and analysis was performed on an intent-to-treat basis.

Overall, the rates of cardiovascular events were not significantly different for the placebo and tamoxifen groups. There were 72

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events among the 6590 tamoxifen users and 68 among the 6604 placebo patients. This represents a relative risk (RR) of 1.06 for tamoxifen users. Furthermore, there were no differences between groups in types of cardiovascular events (ie, fatal/nonfatal MI, and stable/unstable angina). In the cardiac high-risk participants, there were 44 events, with 25 in the tamoxifen group and 19 in the placebo group (RR = 1.39). In the low-risk cardiac group, there were 96 events, with 47 events in the tamoxifen group and 49 in the placebo group (RR = 0.96).

Reis et al concluded that their study, the largest reported cardiovascular study of a nonsteroid-related compound in women, did not show a cardiac-related treatment effect.

COMMENT BY EDWARD J. KAPLAN, MD

Approximately 1 in 3 women, or nearly 500,000 annually, will die of heart disease. In contrast, 1 in 9 women will develop breast cancer, and 1 in 25 will die of it. Estrogen loss associated with menopause has been associated with an elevated risk of cardiac events. The Heart and Estrogen/Progestin Replacement Study (HERS) Research Group conducted a prospective, placebo-controlled trial of hormone replacement therapy with conjugated estrogens and medroxyprogesterone acetate in women with documented coronary disease that was reported by Hulley et al.[2] Despite no statistically significant difference in numbers of myocardial infarctions or cardiac deaths in the treatment and placebo groups, there was a statistically significant time trend noted. There were more cardiac events in the hormone replacement group in the first year but fewer in the fourth and fifth years. This finding raised the issue of the possibility of a similar phenomenon in tamoxifen-treated patients.

Tamoxifen is a nonsteroidal compound that possesses mixed estrogen agonist and antagonist properties. It has known anti-atherosclerotic effects, such as the lowering of low-density lipoprotein (LDL) levels and an increase in high-density lipoprotein (HDL) concentrations. It also has beneficial effects on coronary artery endothelial cells. However, based on the HERS data, it was felt that tamoxifen might exert estrogen antagonist properties on the coronary vasculature that could contribute to myocardial ischemia and thereby induce cardiac events.

The NSABP data as outlined by Reis et al failed to show any influence by tamoxifen on the incidence of cardiac events in either the high- or low-risk cohorts studied. Unlike the HERS trial, no time trend was identified based on cumulative incidence curves, and there was no offsetting of an early adverse effect of tamoxifen by a late beneficial effect.

Two earlier trials randomized breast cancer patients to tamoxifen vs. no adjuvant therapy to evaluate the effect on cardiac health. The Scottish trial enrolled 1070 postmenopausal women who were randomized to tamoxifen 20 mg q.d. × 5 years vs. no adjuvant therapy and found a statistically significant reduction in cardiac death rate associated with tamoxifen.[3] The end point in that trial excluded nonfatal cardiac events along with cardiac events that may have occurred after any recurrence of breast cancer, and so the usefulness of the results may be somewhat limited. The Stockholm Breast Cancer Study Group trial of 2365 postmenopausal early- stage breast cancer patients randomized participants to tamoxifen 40 mg q.d. vs. no adjuvant therapy and found no significant difference in cardiovascular effects.[4]

Reis et al described several potential pitfalls in the design of the NSABP study. The major drawback of the study is that the evaluation of cardiac effects was a secondary goal, and the trial was, in fact, not designed to detect differences in incidences of cardiac events. In

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addition, division of participants into study groups was based on self-reporting, which can be flawed. The 76% compliance rate with tamoxifen assignees may have diluted the ability to detect an effect. Finally, the follow-up period may have to be longer in order to determine the long-term cardiac effects of tamoxifen.

For the reasons cited above, Reis et al stated that they cannot conclude with statistical certainty that there are no cardiac-related treatment effects associated with tamoxifen, but, as mentioned by Jordan in an accompanying editorial,[5] tamoxifen for the chemoprevention of breast cancer seems to provide a better safety profile than hormone replacement therapy in women at risk for coronary disease. ❖

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Predicting Sentinel Node Involvement By Melanoma Histology

ABSTRACT & COMMENTARY

Synopsis: *Histopathological features of ulceration and lymphovascular invasion were found to predict the presence of metastatic melanoma in a series of 105 patients with resected sentinel nodes. Even more important, however, was the thickness of the primary lesion. Histological features may improve predictive power, but absence of these negative factors does not exclude the possibility of nodal spread, and sentinel node dissection is recommended for all patients with primary lesions of 1 mm or greater.*

Source: Nguyen CL, et al. *Am J Surg*. 2001;181:8-11.

The role for sentinel node mapping remains to be established in the management of melanoma. The purpose of the current study from the Medical University of South Carolina was to determine whether certain primary histopathological features of resected melanoma would predict sentinel lymph node status. This information might be used to identify those patients with primary melanoma for whom lymphatic mapping and sentinel lymphadenectomy would be of no benefit.

One hundred twelve patients underwent sentinel node biopsy between May 1995 and August 1999, and sentinel nodes were identified in 105 (94%). Routine histology and immunohistochemistry (to detect HMB-45 and S-100 antigens) were performed on all resected nodes. Of the 7 patients who had undetected sentinel nodes, 3 went on to have formal lymph node dissections, and no evidence for disease was found in any of these 3 patients. Of the 105 sentinel nodes, metastatic melanoma was discovered in 21 (20%). Eighteen of the 21 patients with positive sentinel nodes underwent subsequent lymph node dissections, and additional positive nodes were found in only 3 (17%). Of the 84 patients with negative sentinel nodes, 2 subsequently returned with lymphadenopathy at 7 and 18 months after sentinel lymphadenectomy, indicating at least a 2.4% false-negative rate. Multivariate analysis revealed that tumor thickness greater than 1.5 mm ($P = .01$), ulceration ($P < .01$), and lymphovascular invasion ($P = .05$) predicted the presence of micrometastases. Other prognostic factors that have proven relevant in the Clark melanoma classification system,[1] such as a high mitotic rate, the presence of regression, and the absence of tumor-infiltrating lymphocytes were found to have no individual predictive value for occult lymph node involvement. Likewise, clinical factors such as gender and melanoma location were analyzed separately by univariate regression and were found to lack significance.

Thus, Nguyen and colleagues concluded that the presence of these unfavorable histological characteristics (ulceration and lymphovascular invasion) may identify a group of patients with thin melanomas who would benefit from sentinel lymphadenectomy.

COMMENT BY WILLIAM B. ERSHLER, MD

In this series of patients with melanoma, sentinel nodes were positive in 20%, and the most important factor was the depth of the primary melanoma. None of the patients with melanomas less than 1 mm were positive, whereas more than 50% of those with thickness greater than 3 mm were positive. In addition to thickness, certain histological features, including ulceration and lymphovascular invasion predicted sentinel node positivity. Thus, tumor thickness of greater than 1.5 mm and the presence of ulceration and lymphovascular invasion were highly predictive of sentinel node involvement. However, in a small number of patients, sentinel nodes were present in patients with primary tumor thickness of 1.1 mm, and in 2 of these cases, there were no unfavorable histological features. Thus, a conservative approach

would be to proceed with the sentinel node sampling in all patients with tumor thickness of 1 mm or more.

An interesting feature of this study was that of the 18 patients with sentinel node positivity that went on to have regional lymphadenectomy, only 3 were found to have additional nodes positive. This is not different from other published reports and may indicate a step-like progression of regional metastases that may be of clinical relevance.[2,3] It is possible that resection of sentinel nodes will have the same effect as more extensive lymphadenectomy with regard to the relevant issues of disease-free and overall survival. However, this conclusion should not be drawn from the current or previous reports but awaits a randomized, controlled clinical trial. In the meantime, it would seem prudent to perform sentinel lymph node dissection in all patients with primary tumors of 1 mm or more, and lymphadenectomy in those with sentinel node positivity. ❖

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CEA, CA 19-9, and CA 72-4: Value Added in Predicting Recurrence of Gastric Cancer

ABSTRACT & COMMENTARY

Synopsis: *Recurrent gastric cancer after primary resection is both common and difficult to treat. One reason is that routine follow-up strategies often miss early recurrence, and, by the time of diagnosis, effective treatment is not available. In the current analysis, 3 tumor markers (CEA, CA 19-9, and CA 72-4) were shown, in aggregate, to be highly sensitive indicators of disease recurrence (87%). Furthermore, CA 72-4 proved also to be highly specific (97%), in that elevations were highly predictive of recurrent disease. Thus, routine use of these tumor markers would likely result in earlier recognition of recurrent gastric cancer, and this may have clinical value if effective treatments can be developed for this earlier stage of recurrent disease.*

Source: Marrelli D, et al. *Am J Surg.* 2001;181:16-19.

Despite curative intent surgery, gastric cancer commonly recurs. The diagnosis of recurrent disease is often delayed and subsequent treatment is frequently ineffective. Earlier recognition of recurrence may allow more effective therapy. The purpose of the current study was to evaluate the effectiveness of the serum tumor markers CEA, CA 19-9, and CA 72-4 in the early diagnosis of recurrence of gastric cancer. One hundred thirty-three patients who had potentially curative surgery at the University of Sienna (Italy) between the years 1988-1995 were included in this analysis. Serum tumor markers were obtained preoperatively, 1 week after surgery, and at regular intervals thereafter.

Preoperatively, CEA was elevated in 16% of patients, CA 19-9 in 35%, and CA 72-4 in 20%. The overall combined sensitivity was 51%. Of the 133 patients included in the study, 75 (56%) had tumor recurrence with a mean time interval of 18 ± 15 months. Of the 75 patients, CEA was elevated at the time of recurrence in 33 (sensitivity 44%), CA 19-9 was elevated in 42 (sensitivity 56%), and CA 72-4 was elevated in 38 (sensitivity 51%). An increase in at least 1 of the markers was observed in 65 patients (overall sensitivity, 87%). The increase in tumor markers preceded (by an average of 5 months) clinical diagnosis of recurrence in 46 cases. In 19, tumor markers became elevated at a time when recurrence was evident by clinical parameters.

In the 58 patients who did not develop recurrent disease during this analysis, CA 72-4 remained low in all but 2 (specificity, 97%). On the other hand, both CEA and CA 19-9 yielded a higher number of false-positives (CEA in 12 cases and CA 19-9 in 15 cases), and, therefore a lower specificity (79% and 74%, respectively). The positive predictive value of CEA, CA 19-9, and CA 72-4 for tumor recurrence was 73%, 74%, and 95% respectively.

Marrelli and colleagues concluded that the combined assay of CEA, CA 19-9, and CA 72-4 may be useful for diagnosis of recurrence of gastric cancer, but they warned that only CA 72-4 positivity should be considered a specific predictor of tumor recurrence.

COMMENT BY WILLIAM B. ERSHLER, MD

The striking findings in this report are 2-fold. First, all patients with preoperative elevations who relapsed did so with an associated reappearance of the tumor markers. Of those who recurred with normal markers (n = 10), all had normal markers prior to tumor resection. Accordingly, one potential application of this finding is to develop a follow-up strategy in which patients with positive preoperative markers simply have periodic reassessment of the panel of markers and proceed with more thorough clinical radioimaging studies only at the time of reappearance of an elevated level. On the other hand, the follow-up protocol for patients showing negative preoperative levels

would include periodic scanning or other instrumental examinations in addition to the tumor markers.

The second important finding is the relatively high specificity of the CA 72-4 assay, as has been reported by other groups.[1,2] Whereas both CEA and CA 19-9 frequently yielded false-positive results, CA 72-4 was shown to be highly specific (97%), and a pathological increase in serum levels was highly predictive of tumor recurrence.

Although inherently appealing, the value of early recognition of recurrent gastric cancer remains to be established. That is because treatment programs for recurrent disease have not typically been successful. Possibly, early recognition will identify some patients with resectable disease, particularly those with local recurrence at the gastric stump. Furthermore, although currently available chemotherapy regimens have met with little success, it is possible that an earlier diagnosis, with presumably a lower tumor burden, might offer more favorable treatment outcomes. One might envision, for example, initiation of an aggressive treatment regimen at the first sign of elevated CA 72-4. Certainly, this is a question that may effectively be answered by careful clinical investigation. ❖

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Anagrelide and Essential Thrombocythemia: How Long?

ABSTRACT & COMMENTARY

Synopsis: *Essential thrombocythemia is a chronic myeloproliferative disorder that, left untreated, is associated with hemorrhagic or thrombotic complications. Several drugs have been shown to lower platelet counts and reduce the occurrence of these complications over the short term. This report is the first concerning long-term treatment with anagrelide in young patients. The common side effects of this drug diminished with time—some patients developed anemia—but in general it was well tolerated and effective for the 10 plus years of treatment.*

Source: Storen EC, Tefferi A. *Blood*. 2001;97:863-866.

Of the chronic myeloproliferative disorders, essential thrombocythemia (ET) has the most favorable prognosis.[1] This is, in part, because it carries the least potential to transform into acute leukemia. Thrombotic or hemorrhagic complications are known to occur, particularly in those patients for whom the platelet count is not maintained below 600×10^9/L. Various treatments have been used to reduce platelet counts in this disorder, including hydroxyurea, busulfan, alpha interferon, and, more recently, anagrelide, and these have been successful in reducing thrombotic and hemorrhagic complications over the short course. However, experience with long-term therapy has been tempered by the risk of acute leukemia development, at least for those receiving busulfan and hydroxyurea. Anagrelide (Agrylin—Shireus), an oral imidazo-quinazoline derivative, was licensed in 1997 for treatment of ET, and it holds the theoretical advantage of not being leukemogenic.[2] Short-term toxicity has been manageable for most, and toxicities include headache, fluid retention, and nausea.[3] Anagrelide is effective in reducing platelet counts in the great majority of ET patients, and this has been shown to reduce thrombotic and hemorrhagic complications for those with the disorder.[3,4]

In the study recently published from the Mayo Clinic, 35 patients who received anagrelide before 1992 were evaluated. All patients were younger than 50 years of age at the time of treatment initiation (older patients were deliberately excluded from this analysis). Anagrelide treatments were adjusted on an individual basis, but the average starting dose was 2 mg/d (range, 1-10 mg/d), and the average maintenance dose was 2.5 mg/d (range, 1-5 mg/d). Three-quarters of the patients were symptomatic with ET (thrombosis in 20%, hemorrhage in 26%, and vasomotor symptoms in 51%). The median platelet count at the beginning of treatment was 1075×109/L (range, 690-2525×10^9/L).

Of the initially treated 35 patients, 26 (74%) achieved a completed remission and 7 (20%) a partial remission, for an overall response rate of 94%. Over the period of study, 27 of the 33 responding patients had remained on the drug for a median of 10.8 years (range, 7-15.5 years). Two of the initial responders had died (1 from a basilar artery hemorrhage and 1 in a motor vehicle accident) and the other 4 withdrew, primarily because of side effects.

With regard to the long-term toxicity, the following observations were described. Whereas the appearance of initial toxicity (headache, tachycardia, edema, and diarrhea) was common, the occurrence waned with the length of time on the drug. Over the long term, anemia was the only new side effect that emerged, with the average drop in hemoglobin, when compared to pretreatment levels, being 1.2 g/dL. However, 8 patients (24%)

had a more than 3 g/dL drop. Only 3 patients discontinued therapy because of side effects, but dose reductions were documented in an additional 3 patients.

Anagrelide remained effective throughout the treatment period. Seven patients (20%) experienced a total of 10 episodes of thrombosis, and these were found to occur only in those whose platelet count was more than 400×10^9/L. In fact, in 8 of the 10, the platelet count was greater that 600×10^9/L at the time of the thrombotic event. Similarly, there were 4 reported bleeding events, and these occurred only when the platelet count was more than 400×10^9/L.

COMMENT BY WILLIAM B. ERSHLER, MD

This report indicates that the majority of young patients with ET can be effectively and safely treated long term with anagrelide. This is good news because ET is a chronic disease, but with high risk for thrombotic or hemorrhagic events when platelet counts are not reduced. It is gratifying to see that the initial adverse symptom complex (particularly headache and fluid retention) diminish with time. The anemia that develops is of some concern but, at least in this series, was not sufficient to require termination of treatment. (It is a curious note that the cause of the anemia remains unexplained but that it does not appear to be a direct inhibition of erythroid precursors by the drug).

The data cannot be generalized to all ET patients, inasmuch as only those younger than the age of 50 at diagnosis were included. Perhaps older patients on long-term anagrelide will have more substantial side effects or other evidence of toxicity. The older group, however, is also more likely to have catastrophic consequences of thrombocytosis, and continued effective therapy is required.

Anagrelide is, no doubt, a welcome advance for the management of essential thrombocythemia. It is effective in reducing platelet counts and most patients are able to get back in the normal range. More importantly, thrombotic and hemorrhagic complications are greatly lessened in treated patients. Now, it is apparent that long-term therapy is both safe and effective, at least for those patients younger than 50 years. There remain, however, no data that such therapy, or any specific drug therapy for this disorder, improves overall survival. It would take a randomized clinical trial to establish that, but it is unlikely that such will occur any time in the near future. Also needed are data about long-term management in older patients. Perhaps we will see an additional report from the Mayo Clinic group on this topic. ❖

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Human Papillomavirus and Invasive Cervical Cancer

ABSTRACT & COMMENTARY

Synopsis: *The prognosis of cervical cancer in relation to human papillomavirus (HPV) type was evaluated in a population-based series of 399 patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB to IV cervical cancer and with analyzable HPV data from tumor samples. The HPV nucleic acid detection was performed on DNA from paraffin-embedded specimens; overall survival, as well as cervical cancer-specific survival, was determined for each patient. The HPV 18-related cancers had a worse prognosis than the HPV 16-related cancers for patients with FIGO stage IB or II disease. Additional study to determine the mechanism for HPV 18-related cervical cancer may identify novel therapies for clinical testing.*

Source: Schwartz S, et al. *J Clin Oncol*. 2001;19: 1906-1915.

Estimates from the american cancer society for US women are that 12,900 new cases and 4400 deaths will occur due to cervical cancer in the year 2001.[1] These estimates reflect the continued dramatic decrease in cervical cancer incidence and death that has been achieved in US women, and this improvement has been made possible by routine use of the Papanicolaou (Pap) smear for early detection of preinvasive disease.[2] Cervical cancer still remains a major cause of cancer-related mortality in women of reproductive age in many developing countries due to a lack of effective screening programs in these countries.[2] Implementation of routine screening for these women would be anticipated to produce significant improvements in cervical cancer incidence and mortality. In addition, improvements are needed for all women with more advanced and invasive cervical cancers.

The role of infection with oncogenic types of HPV as an initiating event for cervical cancer has been well described.[3] The oncogenic HPV 16 and HPV 18 viruses are found with the greatest frequency in invasive cervi-

cal cancer.[4] An evaluation of prognosis associated with different HPV types could help elucidate the molecular basis of oncogenesis and potentially identify novel treatment strategies.[5-7] The current study was performed to evaluate the association between HPV type and prognosis of patients with invasive cervical cancer.

This study by Schwartz and colleagues evaluated 399 women who had a diagnosis of FIGO stage IB to IV cervical cancer and also had analyzable HPV DNA in archival paraffin-embedded specimens. All of these patients were residents of 3 Washington state counties and had their diagnosis of cervical cancer made between 1986 and 1997. Median time for observation was 50.8 months, and total mortality (TM) and cervical cancer-specific mortality (CCSM) were determined. The cumulative TM of the 86 patients with HPV 18-related tumors was 33.7%, and the cumulative TM of the 210 patients with HPV 16-related tumors was 27.6%. The cumulative CCSM for patients with HPV 18-related tumors was 26.7%, and the cumulative CCSM for patients with HPV 16-related tumors was 18.1%. Hazard ratio (HR) adjusted for age, stage, and histologic type identified an increased risk for TM (HR, 2.2; 95% CI, 1.3-3.6) and CCSM (HR, 2.5; 95% CI, 1.4-4.4) for patients with HPV 18-related cancers compared to patients with HPV 16-related cancers. The strongest association was for patients with stage IB and IIA disease, with significant findings for HR both for TM (HR, 3.1; 95% CI, 2.3-4.2) and CCSM (HR, 5.8; 95% CI, 3.9-8.7). No association was seen for patients with stage IIB to IV disease. Schwartz et al concluded that HPV 18-related cervical cancers have a poor prognosis and speculate that understanding the basis for this poor prognosis may identify novel treatment approaches for these patients.

COMMENT BY MARK R. ALBERTINI, MD

The decline in cervical cancer incidence and mortality in US women represents the successful implementation of an effective screening modality (Pap smear) for a disease with a well-recognized preinvasive stage. Similar successful efforts are needed for women in developing countries, as substantial reductions in cervical cancer incidence and mortality could also be achieved for those women. The association of cervical cancer with HPV infection has allowed for study of the oncogenic process of this disease, and low-risk and high-risk types of HPV infection have been identified.[2] The current study suggests differences in prognosis for cervical cancer depending on the type of high-risk HPV infection with which it is associated. The HPV 18-related cervical cancers are associated with a worse prognosis for patients with FIGO stage IB or IIA disease. It is not clear why the worse prognosis associated with HPV 18-related cancers compared with HPV 16-related cancers was only seen for FIGO stage IB and IIA disease, but not for stage IIB to IV disease. The HPV type may influence aspects of disease related to initial growth and spread of disease. Further study of the molecular pathogenesis of HPV 18 and HPV 16-related cervical cancer is needed and may identify novel strategies for treatment of this disease. ❖

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CME Questions

19. Which of the following tumor markers is considered both moderately sensitive and highly specific for recognizing recurrent gastric cancer?

a. CEA
b. CA 19-9
c. LDH
d. CA 72-4

20. Which of the following statements is true about HPV 16 and HPV 18 infection and the prognosis of invasive cervical cancer?

a. HPV 18-related cervical cancer is associated with a worse prognosis for patients with FIGO stage IIB to IV disease.
b. HPV 18-related cervical cancer is associated with a worse prognosis for patients with FIGO stage IB or IIA disease.
c. HPV 16-related cervical cancer is associated with a worse prognosis for patients with FIGO stage IIB to IV disease.
d. HPV 16-related cervical cancer is associated with a worse prognosis for patients with FIGO stage IB or IIA disease.

21. Based on data from the HERS trial, concerns were raised that tamoxifen might exert:

a a cardioprotective effect.
b. disappointingly little, if any, effect on the heart.
c. a harmful effect on the heart in women without prior cardiac histories.
d. harmful cardiac effects within the first year of use.

22. Reis et al concluded that tamoxifen use:

a. is safe in women without prior cardiac histories but must be

used with caution in women with prior cardiac events.
b. is safe in women taking 40 mg daily for prophylaxis against breast cancer.
c. is safe in women taking 20 mg daily for prophylaxis against breast cancer.
d. cannot be recommended until further studies are done.

23. Which of the following histological features does *not* predict melanoma sentinel node positivity?
a. Mitotic index
b. Tumor thickness
c. Lymphovascular invasion
d. Ulceration

24. Which of the following statements about anagrelide therapy for essential thrombocythemia is true?
a. It has been shown to be safe and remain effective as a long-term treatment for young (< 50 years) patients with this disorder.
b. It has been shown to be safe, effective, and to prolong survival in patients of all age groups with this disorder.
c. It has been shown to be safe and remain effective as a long-term treatment for older (> 65 years) patients with this disorder.
d. It has been shown to be safe, effective, and to prolong survival in young (< 50 years) patients with this disorder.

In Future Issues:

STI 1571: Use in Nonleukemic Malignancies