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COX-2 Expression in Oncology

ABSTRACT & COMMENTARY

Synopsis: *Soslow and colleagues studied the expression of COX-2 in tumor specimens. Whereas COX-1 was constitutively expressed at low levels, COX-2 expression was limited to malignant, premalignant and adjacent nonneoplastic epithelium. The potential for inhibition of COX-2 in oncology is discussed.*

Source: Soslow RA, et al. *Cancer* 2000;89:2637-2645.

Twenty cases each of lung, colon, and breast cancer specimens were randomly obtained for a retrospective analysis of cyclooxygenase (COX) expression as determined by immunohistochemistry. The results were reported as an immunohistochemical score (IHS) ranging from 0-12. The IHS was determined by the product of two numbers representing 1) the percentage of immunoreactive cells (scale 0-4) and 2) the staining intensity (scale 0-3). The IHS was considered strong if this product was 9-12, moderate if 5-8, weak if 1-4, and negative if 0. COX-1 expression was found to be ubiquitous with no variation between benign or neoplastic tissue whereas COX-2 expression varied depending on location.

The 20 lung cancer cases included 16 with adenocarcinoma or large cell carcinoma, the remainder being either squamous cell carcinoma (3) or carcinoid (1). Overall, 90% of the lung cancers expressed significant levels of COX-2. Benign tissue over 2 cm from the malignant tumor showed no COX-2 expression, although 4 out of 14 samples from tissue adjacent to malignant areas did show COX-2 expression.

The 20 cases of colon cancer were all adenocarcinomas with the exception of one neuroendocrine carcinoma. Again, benign tissue over 2 cm from the malignant tumor showed no COX-2 expression. On the other hand, 71% of the adenocarcinomas contained moderate to strong COX-2 expression. The likelihood of COX-2 expression varied with the differentiation of the colon cancer. This ranged from no expression in poorly differentiated tumors to frequent expression in adenomas (86%).

The 20 breast cancer cases contained infiltrating carcinoma (17) or DCIS alone (3). As was seen with the other tumor types, no COX-

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2 expression was found in distant benign tissue. Whereas only 41% of the infiltrating carcinomas expressed COX-2, expression was seen in 80% of DCIS lesions.

COMMENT BY KENNETH W. KOTZ, MD

The formation of prostaglandins from arachidonic acid is catalyzed by the COX enzyme. The well-known anti-inflammatory effects of NSAIDs are mediated by inhibition of COX. The discovery of two COX isoforms led to the ability to specifically inhibit COX-2, allowing for more specific control of inflammation with less side effects. COX-1 is generally thought to be constitutively expressed in many cells and function as a "housekeeping" enzyme, examples including protecting the gastric mucosa and maintaining renal blood flow. On the other hand, COX-2 expression seems to be induced in response to injury or inflammation. Inhibiting COX-2 will result in decreased prostaglandin formation thereby mediating the inflammatory response. The lack of COX-2 expression in locations such as platelets allows for an increased therapeutic ratio. The categorization of the relative roles of COX-1 and COX-2 as "housekeeping" and "inflammatory response" enzymes, respectively, may be oversimplified.[1]

Two COX-2 inhibitors are available in the United States. Rofecoxib (Vioxx) is approved for use in osteoarthritis, acute pain in adults, and primary dysmenorrhea. Celecoxib (Celebrex) is approved for use in osteoarthritis, rheumatoid arthritis, and of particular interest to oncologists, familial adenomatous polyposis (FAP). In this latter disorder, the drug was shown to reduce the number of adenomatous colorectal polyps, but with unproven effects on cancer reduction, morbidity, or mortality. Whereas the dose used in arthritis is 200-400 mg per day, the dose recommended for FAP is 800 mg total per day, increasing the risk of side effects. In a study of 83 patients, the 800 mg total dose reduced polyp formation by 28%, compared with 12% for 200 mg total per day, and 5% for placebo.

Studies of COX-2 inhibition will interest oncologists because of the potential role of COX-2 in neoplastic physiology. First, COX-2 overexpression may prevent normal pathways of apoptosis. Second, COX-2 may promote angiogenesis. Third, COX-2, which can be expressed in response to tumor promoters, may impair immune surveillance possibly through the effects of prostaglandin E_2.[1] Inhibition of these processes may halt the transformation of premalignant lesions and possibly even reverse established malignant behavior. The potential role of COX-2 in the development of malignant clones is suggested by the results of Soslow et al who observed moderate immunoreactivity for COX-2 not only in adjacent nonneoplastic tissue, but also in premalignant lesions (atypical adenomatous hyperplasia of the lung, colonic adenomas, and DCIS of the breast).

There are numerous preclinical studies, some referenced by Soslow et al, that support testing the potential of inhibiting COX-2 in oncologic diseases. In fact, there are several open clinical trials looking at the role of COX-2 inhibition in oncology. Examples include: 1) the use of celecoxib with trastuzumab in women with HER2/neu overexpressing metastatic breast cancer that is refractory to trastuzumab; 2) the use of celecoxib in preventing disease recurrence in patients with bladder cancer; 3) the use of celecoxib to prevent cancer in patients with Barrett's esophagus; and 4) the use of celecoxib to prevent polyp formation in patients treated for sporadic adenomatous polyps. Certainly, it is too early to use COX-2 inhibitors for prevention or treatment of malignant or premalignant conditions outside the context of a clinical trial, but it is certainly exciting to see if the ability to selectively inhibit COX-2 will be useful to the practice of oncology. ❖

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Clinical Oncology Alert, ISSN 0886-7186, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.
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GST Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Clinical Oncology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $37.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

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Subscription Prices

United States
$269 per year (Student/Resident rate: $105).

Multiple Copies
1-9 additional copies: $197 each; 10 or more copies: $175 each.

Canada
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Elsewhere
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Cellular Phones and Brain Cancer: Absence of Proof

ABSTRACTS & COMMENTARY

Synopsis: *There has been widespread use of cellular telephones in the past decade; and a theoretical concern has been raised that this might increase the risk of brain tumors. In the past month, two reports of case control studies failed to demonstrate an increase in risk among cellular telephone users. As reassuring as these reports are, continued epidemiological vigilance is warranted.*

Sources: Muscat JE, et al. *JAMA* 2000;284:3001-3007; Inskip PD, et al. *N Engl J Med* 2001;344:79-86.

The use of cellular telephones has grown remarkably in the last decade and currently there are more than 500 million subscribers to cellular-telephone services worldwide. There has been concern raised that the radiation, or even thermal effects, of cellular telephone use may confer a risk of brain cancer.[1,2] Within the last two months, two substantial case-control studies were published that should allay most concerns over this question.

The first report was from five academic U.S. medical centers and published in *JAMA*. Between 1994-1998, Muscat and colleagues studied 469 patients with primary brain cancer between 18-80 years of age, and 422 matched controls. The main outcome examined was the risk of brain cancer in the context of hours of handheld cellular telephone use per month or years of use. The median hours of use were 2.5 for cases and 2.2 for controls. The multivariate odds ratio (OR) was 0.85 (95% confidence interval [CI] was 0.6-1.2). The OR for infrequent users (< 0.72 h/month) was 1.0 (0.5-2.0) and for frequent users (> 10.1 h/month) was 0.7 (0.3-1.4). The mean duration of use was 2.8 years for cases and 2.7 years for controls. Thus, no association was observed according to duration of use ($P = 0.54$).

The second report, published just two weeks later in the *New England Journal of Medicine* was also a case-control on patients with brain cancer seen in Phoenix, Boston, or Pittsburgh between 1994-1998. There were a total of 782 patients with brain tumors (489 with glioma, 197 with meningioma, and 96 with acoustic neuroma) and 799 controls (patients admitted to the same hospitals for a variety of nonmalignant conditions). As compared with never, or rarely having used a cellular telephone, the relative risks associated with cumulative use of a cellular telephone for more than 100 hours were 0.9 for glioma (0.5-1.6); 0.7 for meningioma (0.3-1.7); 1.4 for acoustic neuroma (0.6-3.5); and 1.0 for all types of tumors (0.6-1.5). There was no evidence that the risks were higher among persons who used cellular telephones for 60 or more minutes per day or regularly for five or more years. Tumors did not occur disproportionately often on the side of the head on which the telephone was typically used.

COMMENT BY WILLIAM B. ERSHLER, MD

Over the past several decades there has been an increase in primary brain cancers that has not been completely explained.[3] A variety of explanations have been proposed, and among them is the increased use of cellular phones.[3] Although of theoretical concern, there had not been any large-scale epidemiological evidence to support the notion that radiation emitted by these devices actually presented a risk for cancer. The current studies found no increased risk, and this should be a reassuring finding.

There are, however, some concerns mentioned in both articles and in the accompanying editorial.[4] Most important among these is the rather long, latent period involved in brain cancer development and the rather short period of widespread use of cellular telephones. Perhaps in future decades there will be increased brain cancers recognized to be causally related to cellular telephones. Furthermore, technology is changing and there has been a shift from analogue to digital equipment. The latter actually uses and emits lower energy, and may possibly be even less of a theoretical risk. Nonetheless, cellular telephone use is becoming so prevalent that exposure is, no doubt, increasing. Thus, continued epidemiological vigilance remains important. As the old adage goes, "absence of proof is not proof of absence." In this regard, two international, multicenter investigations are just getting started. Hopefully, these will continue to demonstrate "absence of proof." ❖

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Natural Killer Cells and Cancer: Immune Surveillance Revisited

ABSTRACT & COMMENTARY

Synopsis: *The presence of immune surveillance against cancer has been difficult to establish in humans. In this longitudinal analysis of a relatively large cohort of individuals for whom a baseline level of lymphocyte (NK cell)-mediated natural cytotoxicity, it was found after 11 years that a lower baseline level of activity was associated with a greater risk for cancer. This report may provide the strongest evidence for the presence of immune surveillance in humans.*

Source: Imai K, et al. *Lancet* 2000;356:1795-1799.

The concept of immune surveillance, originally proposed by Burnet over three decades ago, remains controversial.[1] Although there is an increase in cancer in those with profound immune deficiency, such as in patients with AIDS or those receiving immunosuppressive medications after organ transplantation, the tumors most commonly encountered are those that theoretically reflect immune dysregulation rather than immune deficiency (e.g., lymphoma, leukemia, and Kaposi's sarcoma).[2] However, there have been published reports that would suggest that individuals with diminished immune function, particularly natural cytotoxicity, are at increased risk for development of malignancy.[3,4] In the current report, a large cohort (n = 3500) of people from a single Japanese community were followed for the development of cancer over an 11-year period.

In 1986, 8552 residents (95% of those ≥ 40 years of age) of a single Japanese town (Saitama) were sent an epidemiological questionnaire and, of these, 3625 self-selected individuals (1371 men and 2254 women) agreed to provide peripheral blood samples. The questionnaire topics were those primarily of lifestyle and included dietary habits, cigarette smoking, alcohol ingestion, body weight, and height. Peripheral blood was analyzed for a variety of biochemical and immunological parameters, including natural killer cell activity by standard chromium (51Cr) release assay using K562 leukemia cells as targets. Eleven years later a follow-up survey on cancer incidence and death from all causes was undertaken.

After excluding early cancers (those which occurred within 2 years of the baseline assessment), there were 154 cases of cancer among the 3500 participants. Individuals were analyzed in tertiles based upon the initial cytotoxicity response (low, medium, and high responders). The age-adjusted relative risk of cancer (all sites) was 0.72 (95% confidence interval [CI] 0.45-1.16) for men with high cytotoxic activity, and 0.62 (0.38-1.03) for men with medium cytotoxic activity, taking the risk of those with low cytotoxic activity as reference. For women with high cytotoxic activity, the relative risk was 0.52 (0.28-0.95), and for women with medium cytotoxic activity the relative risk was 0.56 (0.31-1.01). For both sexes with high and medium cytotoxic activity risks were 0.63 (0.43-0.92) and 0.59 (0.40-0.87).

The results were interpreted as supportive of the concept that NK cells mediate resistance to cancer development, as those with low activity were shown to have increased cancer development over this 11-year span.

COMMENT BY WILLIAM B. ERSHLER, MD

Many immunologists have laid to rest the concept of immune surveillance, primarily because its very existence has been difficult to establish in human beings. For one thing, the tumors that develop in profoundly immune deficient people (and animals, for that matter) have been those more reflective of immune dysregulation than immune deficiency. If one were to implicate a failure of immune surveillance as an explanation of the common cancers in the general population, then one would expect a similar pattern of malignancy (e.g., lung, colon, breast, and prostate cancers) in patients with AIDS or after organ transplantation. Or should we? Perhaps those common cancers are associated with a more subtle decline in immune (or natural killer) function and because of their longer preclinical stage (estimated to be a decade or more for most epithelial cancers), their development is just not apparent in patients with AIDS or transplant recipients, many of whom will not live long enough with their illness to develop these cancers.

The Japanese cohort is a remarkable contribution in this regard. A careful analysis of natural cytotoxicity was performed in a relatively large group of adults, some of whom later went on to develop cancer (primarily stomach, lung, and colon). Those with lower baseline cytotoxicity, particularly women, were at significantly greater risk for cancer development. This analysis is perhaps the strongest evidence to date that a decline in lymphocyte function is associated with the occurrence of the common malignancies encountered in the general population. Inasmuch as NK cell function is influenced by lifestyle characteristics (such as chronic stress, dietary habits, and cigarette smoking), positive adjustment of these factors may possibly reduce cancer incidence by

immunological mechanisms. This, of course, is theoretically appealing but totally lacking in scientific documentation. ❖

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High-Dose Cyclophosphamide as Initial Treatment for Aplastic Anemia: Too Toxic

ABSTRACT & COMMENTARY

Synopsis: *High-dose cyclophosphamide has been shown to be effective treatment for severe aplastic anemia. In this report, such treatment was compared with the more conventional approach of antithymocyte globulin. The trial was terminated after three patients in the cyclophosphamide group died within three months of treatment. Thus, although there are theoretical advantages for treatment with high-dose cyclophosphamide in this disorder, these advantages are unlikely to outweigh the increased life-threatening toxicity of such an approach. For the time being, ATG with cyclosporin remains the standard of care for aplastic anemia patients who are not candidates for bone marrow transplantation.*

Source: Tisdale JF, et al. *Lancet* 2000;356:1554-1559.

High-dose cyclophosphamide has been proposed as an effective therapy for aplastic anemia, with a response rate similar to that with regimens containing antithymocyte globulin (ATG), but with more durable remissions and reduced clonal hematological complications.[1,2] These early reports of such treatment have been encouraging, but no direct comparison with ATG-based regimens has been available. Tisdale and colleagues from the National Heart, Lung, and Blood Institute (NHLBI, NIH) performed a phase III, prospective, randomized trial to compare response rates to immunosuppression with either high-dose cyclophosphamide plus cyclosporin or conventional immunosuppression with ATG plus cyclosporin in previously untreated patients with severe aplastic anemia.

Thirty-one patients were enrolled in this study; 15 were assigned cyclophosphamide (1h intravenous infusion of 50 mg/kg daily for 4 days) and 16 were assigned ATG (40 mg/kg daily for 4 days). Both groups also received cyclosporin, initially at 12 mg/kg daily with adjustment to maintain concentrations at 200-400 ug/L, for six months. The primary end point was hematological response (no longer meeting the criteria for severe aplastic anemia and becoming transfusion independent). Analyses were by intention to treat. Secondary endpoints were overall survival, event-free survival, response duration, and evolution to paroxysmal nocturnal hemoglobinuria, myelodysplasia or acute leukemia.

The trial was terminated after three early deaths in the cyclophosphamide group. Median follow-up was 21.9 months for the 31 that were enrolled, and all of these patients had completed their initial immunosuppressive treatment. There was excessive morbidity in the cyclophosphamide group (invasive fungal infections in 4 patients vs none in the ATG group) and three early deaths within the first three months (vs none in the ATG group). There was no significant difference at six months after treatment in the overall response rates among evaluable patients (6/13 [46%] cyclophosphamide vs 9/12 [75%] ATG).

Tisdale et al suggest that cyclophosphamide is a dangerous choice for initial treatment of severe aplastic anemia. However, long-term analysis of these treated patients may demonstrate that remission duration or overall survival will be better for those that have survived the initial treatment with cyclophosphamide. Still, the use of high-dose cyclophosphamide in this setting remains to be established.

COMMENT BY WILLIAM B. ERSHLER, MD

The majority of patients with acquired aplastic anemia may be effectively treated with immunosuppressive therapy and ATG with cyclosporin has produced significant responses in the majority of cases. However, ATG-induced responses have generally been incomplete and relapses are not uncommon. Nevertheless, although incomplete, the responses most frequently result in freedom from transfusions and definitely in prolonged survival.[3] This stated, the promise of high-dose cyclophosphamide as an alternative was a more robust remission, perhaps even cure and the hopeful expectation that relapses would be less common and long-term clonal disorders, such as paroxysmal nocturnal hemoglobinuria, myelodysplasia, and leukemia would occur less frequently. These findings are unlikely to be demonstrated in the current study because the high level of early toxicity, including death in three of 16 treated patients, forced the early termination of the recruitment

phase. Thus, even if these outcomes of the high-dose cyclophosphamide treatment actually occur, it is unlikely there will be a sufficient number of patients in the present trial to establish this with statistical significance.

The use of high-dose cyclophosphamide is unlikely to become the standard of care for severe aplastic anemia. For younger patients with appropriately matched allogeneic bone marrow donors, transplantation remains an appropriate choice. For others, immunosuppression with ATG and cyclosporin is likely to remain the standard of care. New, more selective immunosuppressive approaches are also under development and will soon be in clinical trial. Hopefully, the promises of the early cyclophosphamide trials will be realized with one or several of these new potent immunopharmacological agents. ❖

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Stereotactic Radio Surgery for Multiple Brain Metastases from Renal Cell Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Metastatic renal cell carcinoma can have a variable clinical course with some patients living for long periods of time despite the presence of metastatic disease. It is not uncommon for patients with indolent disease to develop one or more metastatic brain lesions. Surgical removal, especially of single lesions, has been reported to prolong survival in patients with renal cell carcinoma. The experience with management of multiple brain metastases is less well described. In this study, Amendola and colleagues report the results of gamma knife radiosurgery in 22 renal cell carcinoma patients with an average of six metastatic brain tumors. Almost all patients achieved control of the metastatic brain lesions and died of systemic disease. Gamma knife radio surgery or stereotactic radiation should be considered in patients with indolent renal cell carcinoma, even in the presence of multiple CNS metastases.*

Source: Amendola BE, et al. *Cancer J* 2000;6:372-376.

Amendola and colleagues report their experience giving 38 radiosurgery treatments in patients with metastatic renal cell carcinoma to the brain from November 1993 to March 1999. Patients ranged from 38-80 years of age with a median age of 60 years. Previous whole brain radiation had been used in 11 of 22 patients. Four patients had single metastasis and 18 had multiple lesions. The number of lesions that were treated ranged from 1-21 sites with an average of six sites per patient. An average of 3.5 sites were treated per treatment. All patients with newly diagnosed or recurrent brain metastasis from renal cell carcinoma were included in the study regardless of the status of the primary tumor or extra-cranial disease. All but two patients had Karnofsky performance statuses of 70% or more. Only two patients did not have evidence of extra-cranial metastasis. Survival was reported from the date of radio surgery to the date of death. The overall survival for the entire group was 56% at six months and 19% at 24 months. Local control was achieved in 20 of 22 patients with one patient developing radiation necrosis; thus three of the 22 patients (14%) experienced a CNS-related death. The remainder of the patients died from non-neurologic causes. One patient remains alive 63 months after the first radio surgical procedure. One patient with 20 metastatic sites in the brain lived 22 months and died of non-neurologic causes.

COMMENT BY MICHAEL J. HAWKINS, MD

Management of patients with isolated CNS metastasis from renal cell carcinoma is generally straightforward, especially if the patient has indolent systemic disease and is an excellent candidate for surgery or stereotactic radiation.[1,2] Management of patients with multiple CNS metastases is less straightforward. Even though renal cell carcinoma is generally considered a radioresistant tumor, responses to stereotactic or gamma knife radiosurgery clearly occur and effective palliation can be achieved. This study confirms the reports of others, demonstrating the use of radio surgery in selected patients with renal cell carcinoma. The mean tumor volume in the patients treated in this study was 3.9 cc but ranged from 0.1-75.5 cc.

The management of this complication in patients with renal cell carcinoma is even more complex because of the need for corticosteroids to manage the vasogenic edema that typically surrounds these lesions. Corticosteroids have been shown to abrogate the antitumor activity of Interluken-2 in animal models and are generally contraindicated in patients with renal cell carcinoma who are receiving Interluken-2. For patients with a good performance status and an isolated brain metastasis that is easily resected, surgery can often control their disease with minimal use of corticosteroids. Radiosurgery frequently may require prolonged steroid

usage due to edema that is generated following the treatment. Thus, the relative risks of surgery vs. delaying systemic therapy due to a continuing need for steroids need to be balanced when determining the best overall approach to these patients. However, stereotactic radiosurgery should strongly be considered for patients with multiple CNS metastases and relatively indolent systemic disease. ❖

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Fine-Needle Aspiration Monitoring of Breast Cancer Treatment

ABSTRACT & COMMENTARY

Synopsis: *The cytologic responses in breast cancers during the 96 hours following the first dose of a preoperative (neoadjuvant) paclitaxel chemotherapy regimen were evaluated in a pilot study using serial fine-needle aspirations (FNAs). Eleven women receiving neoadjuvant chemotherapy with paclitaxel (200 mg/m^2 every 2 weeks for a total 4 cycles) for primary breast cancer of at least 2 cm in greatest diameter received serial FNAs before treatment and at 24, 48, 72, and 96 hours after the first paclitaxel dose. Apoptotic and mitotic indices were determined in breast cancer cells from the FNA samples, and the cumulative apoptotic response during the first 96 hours after the first dose of paxlitaxel had an almost linear relationship with the extent of tumor reduction. Serial FNAs provide a minimally invasive strategy to evaluate in vivo cellular responses to chemotherapy and may allow for development of chemopredictive assays.*

Source: Symmans WF, et al. *Clin Can Res* 2000;6: 4610-4617.

Neoadjuvant chemotherapy is given to women with locally advanced primary breast cancer to reduce tumor size for subsequent surgical management and to predict patient outcome based on the observed preoperative chemotherapy response.[1,2] Use of neoadjuvant chemotherapy can result in a pathologic complete response (pCR) of invasive breast cancer in the breast and axillary lymph nodes, and patients with a pCR have improved disease-free survival compared with patients who fail to achieve this outcome.[3] Conventional measures of treatment response, such as physical exam, mammography, and breast sonography, have not been able to accurately and consistently predict pathologic response to treatment.[4-6] Thus, a predictive biomarker of treatment response could be useful for the management of these patients.

Symmans and colleagues report results of a pilot study involving 11 patients with primary breast cancer without evidence of systemic metastases and a breast tumor of at least 2 cm. The patients received neoadjuvant paclitaxel chemotherapy (200 mg/m^2 every 2 weeks for a total of 4 cycles) and monitoring that included a baseline FNA as well as serial FNAs 24, 48, 72, and 96 hours after the first paclitaxel infusion. Clinical and radiological measurements of the primary breast tumor were made prior to paclitaxel as well as preoperatively following the fourth cycle of paclitaxel. The cellular samples from the FNAs were fixed in 95% ethanol and stained with H&E. Apoptotic cells were identified following staining with H&E, and an apoptotic and mitotic index were determined at each timepoint. The background heterogeneity of these measurements was shown by analysis of apoptotic and mitotic indices in a separate group of seven untreated resected invasive breast cancers.

Patients received an initial FNA prior to receiving paclitaxel neoadjuvant therapy. The apoptotic and mitotic indices in these baseline samples did not correlate with the proportion of residual tumor following treatment. Patients then received FNAs 24, 48, 72, and 96 hours after the first paclitaxel infusion. The apoptotic response to the first dose of paclitaxel did correlate with the proportion of residual cancer following the neoadjuvant treatment. This inverse correlation of relative change in apoptotic index (compared with the pretreatment index) with residual cancer volume occurred at each of the four timepoints after the first paclitaxel dose and was even greater when a cumulative apoptotic response was calculated for days 1-4. No correlation was present between the cumulative mitotic response and the proportion of residual cancer after the neoadjuvant paclitaxel therapy. Symmans et al conclude that larger clinical studies are indicated to validate use of the apoptotic response as a predictive biomarker for breast cancer tumor response to paclitaxel neoadjuvant therapy.

COMMENT BY MARK R. ALBERTINI, MD

Paclitaxel is a taxane with demonstrated activity against breast cancer.[7] A preclinical murine model of paclitaxel therapy identified peak apoptotic index and pretreatment apoptotic index as it correlates with murine tumor reduction.[8] A similar predictive biomarker for

breast cancer response to paclitaxel neoadjuvant therapy could be clinically useful for management of patients with locally advanced breast cancer. Symmans et al proceeded with the current study to determine potential use of serial FNA to determine apoptotic response as a guide for treatment of patients receiving paclitaxel neoadjuvant therapy. Results from this small pilot study demonstrate feasibility of this approach and suggest that meaningful biologic data can be obtained with this minimally invasive procedure.

The apoptotic response to a single dose of paclitaxel lasted for about four days in patients treated on this study. The potential relevance of this observation for decisions about paclitaxel scheduling requires clinical investigation. The cumulative apoptotic response during the initial 96 hours following the first dose of paclitaxel had an almost linear relationship with tumor reduction. While this observation requires confirmation in a larger study, the possibility exists for an early biomarker for antitumor response in these patients. Thus, decisions about timing of surgery or changes in chemotherapy regimens may be possible earlier in the course of the patient's treatment. Patients without a significant apoptotic response to an initial dose of paclitaxel could be identified as candidates for alternate neoadjuvant strategies or earlier surgical intervention.

The use of FNA monitoring of tumor cells during therapy may allow for investigation of resistance mechanisms to treatment as well as to identify predictive biomarkers of tumor response. This approach is minimally invasive and offers the possibility of increasing our knowledge of breast cancer cellular responses during therapy. While monitoring apoptosis may or may not be confirmed as a predictive biomarker for paclitaxel neoadjuvant therapy, this FNA monitoring strategy merits further clinical investigation in this as well as additional clinical settings. ❖

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CME Questions

7. Which of the following is true?
a. COX-1 expression is inversely related to COX-2 expression.
b. Overexpression of COX-2 is a prerequisite step for malignant transformation of adenomatous polyps.
c. Inhibition of COX-2 reduces the number of cancers in familial adenomatous polyposis.
d. Inhibition of COX-2 reduces the number of polyps in familial adenomatous polyposis.

8. Which of the following statements about high-dose cyclophosphamide treatment for aplastic anemia is true?
a. It is more effective in producing remissions.
b. It produces more long-term toxicity (i.e., toxicity apparent one year after treatment).
c. It produces more acute toxicity (i.e., toxicity apparent within the first three months after treatment).
d. It is a more effective and less toxic approach than ATG with cyclosporin.

9. The frequent use of cellular telephones has been associated with:
a. an increased risk of benign brain tumors.
b. an increased risk of gliomas.
c. an increased risk of acoustic neuromas.
d. All of the above
e. None of the above

10. Which of the following lymphocyte populations is likely to be associated with some degree of protection from cancer development?
a. CD4+ T cells
b. CD8+ T cells
c. B cells
d. NK cells

11. Which of the following statements is *false* about an apoptotic response in breast cancer cells?
a. It can be detected within 96 hours following an initial dose of neoadjuvant paclitaxel therapy.
b. It may correlate with the extent of tumor reduction following an initial dose of neoadjuvant paclitaxel therapy.
c. It can be detected in samples obtained by FNA.
d. It is quite homogeneous within a given breast tumor sample.

12. A disadvantage to the use of stereotactic radiosurgery in the treatment of CNS metastases from renal cell carcinoma is:
a. only single lesions may be treated.
b. local control is rarely achieved due to the radioresistance of renal cell carcinoma.
c. radionecrosis occurs frequently and is often the cause of death.
d. treatment may exacerbate the peritumoral edema requiring prolonged use of corticosteroids, potentially delaying initiation of systemic therapy with IL-2.

In Future Issues:

High or Standard Dose Chemotherapy for Non-Hodgkin's Lymphoma