AMERICAN HEALTH CONSULTANTS®

CLINICAL ONCOLOGY ALERT

A monthly update of developments in cancer treatment and research

2000 index enclosed with this issue

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

Surgical Palliation of Renal Cell Carcinoma Metastatic to Bone

ABSTRACT & COMMENTARY

Synopsis: *Management of boney metastasis from renal cell carcinoma is often problematic. These lesions may be extremely painful and may exhibit only in marginal response to radiation therapy. The natural history of metastatic RCC can be highly variable with some patients living more than five years with metastatic disease. Successful palliation of these boney lesions can often result in a markedly improved quality of life. Kollender and colleagues report on the outcomes of surgical management of boney metastasis in 45 highly selected patients with metastatic RCC. Pain relief and a good to excellent functional outcome was achieved in approximately 90% of the patients. Reflecting the selection process, approximately half of the patients lived more than two years and 38% lived more than three years.*

Source: Kollender Y, et al. *J Urol* 2000;164:1505-1508.

Management of renal cell carcinoma (rcc) to the bone is frequently problematic due to the relative radio-resistance of these lesions. Between 1980 and 1997, 45 patients with a total of 56 lesions underwent surgery for metastatic RCC of the bone. Indications for surgery were a solitary bone metastasis (11 cases), interactable pain (24 cases), or impending/pathological fracture (21 cases). A wide excision (29 cases) consisting of en-block removal of the tumor with margins of normal bone and soft tissue was performed when bone destruction was extensive or when there was a solitary bone metastasis. Marginal excision with cryosurgery (25 cases) was performed when the circumferential realm of cortex remaining after tumor removal was sufficient to ensure a stable reconstruction. This technique involved curettage with adjuvant freezing of the tumor cavity with liquid nitrogen. Amputation was done when there was massive tumor extension to the soft tissue with invasion of a major neurovascular bundle of the extremity (2 cases). In those patients for whom amputation was not planned, preoperative embolization of the lesion was typically performed to decrease interoperative blood loss. Three patients who underwent marginal resection with cryotherapy also received postoperative adjuvant radiation therapy. No patient had more than 600 cc of

Volume 16 • Number 1 • January 2001 • Pages 1-8

INSIDE

blood loss from an extremity lesion or 1200 cc from a pelvic lesion. There were no incidences of flap necrosis, deep wound infection, nerve palsy, or thromboembolic complications. Mean hospital stay was 9.8 days (range, 6-21 days). Of 34 patients with disease in the pelvic girdle or lower extremities, 34 (94%) were ambulatory postoperatively. The remaining two patients were wheelchair bound. Forty-one patients (91%) had significant pain relief and function was estimated to be good or excellent in 89%. Four lesions recurred, including three after marginal excision. Radiation therapy was administered for two of the recurrent lesions, but the remaining two were asymptomatic and occurred preterminally. Of the 11 patients with a solitary metastasis, 73% lived more than three years. However, only 25% of those patients who underwent surgery for intractable pain or for an impending or pathological fracture lived more than three years.

COMMENT BY MICHAEL J. HAWKINS, MD

Patients with metastatic RCC to bone often present difficult management decisions for a medical oncologist. While a systemic, usually immunologically induced, complete remission is the most desirable outcome, most patients do not respond to interleukin-2 administered either alone or in combination with interferon-alpha and/or chemotherapy. It is well recognized that metastatic RCC can have a highly variable course. It is not uncommon for patients to be completely or relatively asymptomatic despite the presence of slow growing metastatic disease. In the face of widespread but slow growing disease, the development of a painful boney metastasis is often treated with radiation. The relative radioresistance of RCC is well recognized, and it is not uncommon for patients to continue to have pain and/or progressive bone destruction despite radiation therapy. In highly selected patients, an aggressive surgical approach is indicated. Patients whose only site of metastatic disease is in the bone can typically be treated surgically with a local control rate that exceeds 90%. When patients have developed extremely painful or mechanically unstable bone metastasis, selection for surgery needs to be weighed with their length of anticipated length of survival. Even though only approximately 25% of the patients in this series lived for more than two years, when they were operated on for these indications significant palliation of symptoms was consistently achieved. The use of adjuvant cryotherapy has resulted in good local tumor control despite less extensive surgical procedures and permits a greater incidence of limb sparing. ❖

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.
EDITORIAL GROUP HEAD: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
ASSOCIATE MANAGING EDITOR: Robin Mason.
COPY EDITOR: Robert Kimball.

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.

AMERICAN HEALTH CONSULTANTS™
THOMSON HEALTHCARE

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail Address:
customerservice@ahcpub.com

Editorial E-Mail Address:
robert.kimball@ahcpub.com

World-Wide Web: http://www.ahcpub.com

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
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 20 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

For CME credits, add $50.

Questions & Comments

Please call Robin Mason, Associate Managing Editor, at (404) 262-5517 or Robert Kimball, Copy Editor, at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Ershler is on the speaker's bureau for Wyeth and does research for Ortho Biotech. Dr. Roberts is a contractor for Eli Lilly and Agouron and is a consultant for Novartis Inc. Pharmaceuticals. Dr. Kotz serves on the speaker's bureau of Rhône-Poulenc Rorer. Dr. Albertini does research for Powder Ject vaccines, Inc and Lexigen Pharmaceuticals.

Tamoxifen Inhibits Second Breast Cancers in Women with BRCA Mutations

ABSTRACT & COMMENTARY

Synopsis: *In a matched, case-control study of women with BRCA1 or BRCA2 mutations and primary, invasive breast cancer, the occurrence of a second breast cancer was significantly reduced if tamoxifen had been used in the treatment of the primary cancer.*

Source: Narod SA, et al. *Lancet* 2000;356:1876-1881.

Women with brca1 or brca2 mutations have a higher incidence of primary breast cancer and of contralateral breast cancer than in those with earlier breast cancer.[1] Tamoxifen protects against contralateral breast cancer in the general population,[2] but it remains to be established whether tamoxifen will reduce the incidence of contralateral breast cancer in patients with

BRCA-associated primary breast cancer. In the study of women with breast cancer and mutations of BRCA1 or BRCA2, tamoxifen use was examined for those who went on to develop a second breast cancer (n = 209) and for those who remained free of a second breast cancer (n = 384). This was a matched, case-control study and tamoxifen use was determined either by interview or by self-administered questionnaire.

The multivariate odds ratio for contralateral breast cancer associated with tamoxifen use was 0.50 (95% confidence interval [CI] 0.28-0.89). Tamoxifen protected against contralateral breast cancer for carriers of BRCA1 mutations (odds ratio 0.38, 95% CI 0.19-0.74) and for those with BRCA2 mutations (0.63, 0.20-1.50). Thus, in women who used tamoxifen for 2-4 years, the risk of contralateral breast cancer was reduced by 75%. As expected, the risk of contralateral breast cancer was also reduced by oophorectomy (0.42, 0.22-0.83) and by chemotherapy (0.40, 0.26-0.60).

COMMENT BY WILLIAM B. ERSHLER, MD

This was a multi-institutional investigation from the Hereditary Breast Cancer Clinical Study Group and there were 1243 living patients with invasive breast cancer in carriers of pathogenic BRCA1 or BRCA2 mutations. Of these, 24% had bilateral breast cancer. A quarter of those with bilateral breast disease were removed from further analysis, primarily because the diagnoses were either synchronous or very close in time, making it impossible to judge the effect of tamoxifen on the second tumor. The remaining 209 cases were matched with others of similar age (within 5 years) with similar mutation (BRCA1 or BRCA2) and similar length of follow-up evaluation. The frequency and mean duration of tamoxifen use were compared between bilateral disease cases and controls. Only 22 (11%) of those with bilateral disease had used tamoxifen compared to 21% of those in the control (unilateral) group.

The findings are important but not unexpected. It has been reported that oophorectomy in patients with BRCA1 mutations and breast cancer reduces the risk of second breast cancer,[3] and that pregnancy increases the risk of cancer for these individuals.[4] However, it is interesting to note that in this analysis, tamoxifen seemed to have a protective effect, even in women who had previous oophorectomy, suggesting an additive effect that may even be independent of receptor-mediated estrogen blockade.

The question remains as to what is the optimal treatment for women with hereditary breast cancer associated with BRCA1 or BRCA2 mutations. It appears from this study that tamoxifen alone will prevent (or, at least delay) the onset of a second breast cancer. Whether the effect is truly additive to that of chemotherapy in this setting, and for how long tamoxifen should be continued are questions that remain unanswered. The latter is indeed one that needs prompt attention with the apparent increased risk of endometrial cancers in long-term tamoxifen users.[4] ❖

References

1. Narod SA, et al. *Am J Hum Genet* 1995;56:254-264.
2. Fisher B, et al. *J Natl Cancer Inst* 1998;90:1371-1388.
3. Rebbeck TR, et al. *J Natl Cancer Inst* 1999;91: 1475-1479.
4. Bergman L, et al. *Lancet* 2000;356:881-887.

Microsatellite Instability in Colorectal Cancer

ABSTRACT & COMMENTARY

Synopsis: *The presence of high-frequency microsatellite instability in colorectal cancer was found to be associated with proximal location, a medullary or mucinous histologic pattern, infrequent p53 expression, and an improved survival compared with tumors that had low-frequency microsatellite instability.*

Source: Gafa R, et al. *Cancer* 2000;89:2025-2037.

Colorectal carcinomas with high-frequency microsatellite instability (HF-MSI) are believed to possess unique biologic properties compared with tumors that have low-frequency microsatellite instability (LF-MSI) or tumors that are microsatellite stable (MSS). The aim of this study was to correlate the presence of HF-MSI with clinicopathologic information.

Gafa and colleagues evaluated 216 surgically resected specimens half of which were proximal to the splenic flexure and half of which were distal. Tumors of any stage were included but not from patients with known inherited colorectal cancer syndromes. In addition to standard histopathologic evaluation, the tissue also underwent microsatellite analysis, immunohistochemical analysis, and flow cytometric DNA ploidy analysis. Tumors were designated as having HF-MSI if three or more of the six analyzed microsatellite loci demonstrated instability, which occurred in 20% of the cases. Immunohistochemistry was used to define the expression of the p53, hMLH1, and hMSH2 proteins.

When the clinicopathologic characteristics of HF-MSI

and LF-MSI/MSS tumors were compared, a number of observations were made concerning tumor location, pathologic subtypes, patterns of local growth, and the likelihood of distant metastases. For example, HF-MSI tumors were localized to the right and transverse colon 90% of the time, whereas LF-MSI/MSS tumors were localized to the distal colon 60% of the time. Furthermore, these HF-MSI tumors were much more likely than LF-MSI/MSS tumors to have a medullary or mucinous pattern or a conspicuous lymphoid reaction. Furthermore, the HF-MSI tumors were far less likely to demonstrate an infiltrating growth pattern or extramural venous invasion. All of these observations were highly statistically significant.

Other interesting pathologic observations were presented. For example, 82% of the HF-MSI tumors were diploid with infrequent p53 overexpression (23%) suggesting that these tumors would have a better prognosis. On the other hand, 80% of the LF-MSI/MSS adenocarcinomas were aneuploid with 54% overexpressing p53.

These pathological observations were supported by clinical findings as well. Considering only those tumors located proximally, distant metastases were present at diagnosis in only 5% of tumors with HF-MSI vs. 24% of tumors with LF-MSI/MSS. Furthermore, only 16% of patients with HF-MSI tumors died of colorectal cancer compared with 44% of patients with LF-MSI/MSS tumors. Considering just the poorly differentiated cancers, the prognosis was markedly improved if the tumor had HF-MSI. This is illustrated by the five-year survival for poorly differentiated tumors of only 37% for cases with LF-MSI/MSS, which jumped to 79% for cases with HF-MSI.

COMMENT BY KENNETH W. KOTZ, MD

There are two genetic pathways that can lead to colorectal cancer. The most common is the "suppressor pathway" characterized by the sequential inactivation of tumor-suppressor genes such as APC, p53, and DCC. This pathway involves marked chromosomal changes with frequent cytogenetic abnormalities.

The other genetic pathway leading to colorectal carcinoma is characterized by widespread microsatellite instability. This "mutator" pathway leads to an accumulation of somatic alterations of simple, repeated sequences called microsatellites. When greater than 30% of microsatellites demonstrate instability, this is called high-frequency microsatellite instability, a consequence of defects in the DNA mismatch repair system. These defects are usually caused by inactivation of the DNA mismatch repair genes. The well-described hereditary nonpolyposis colon cancer syndrome is caused by mutations (rather than inactivation) of DNA mismatch repair genes. Like tumors with HF-MSI, proximal orientation in the bowel has also been noted in this syndrome.

The study by Gafa et al has provided some interesting clinicopathologic findings. First, the majority (86%) of tumors with a medullary pattern had HF-MSI. Second, the HF-MSI tumors were highly likely (90%) to occur in the proximal colon. Third, despite the poor differentiation, patients with HF-MSI tumors actually had a better prognosis than LF-MSI/MSS tumors.

The mechanism behind the improved prognosis afforded HF-MSI tumors is unknown. Perhaps the multiple mutational changes lead to an immune response against new tumor-associated antigens or alternatively these multiple genetic changes might simultaneously place these malignant cells at a growth disadvantage. Whereas loss of classic tumor suppressor genes is often associated with tumor progression and an increased ability to spread (which requires angiogenesis and breakdown of the cell membrane), it may be that HF-MSI predominantly imparts a local growth advantage to the tumor.

The ultimate clinical significance of measuring microsatellite instability in colorectal cancer remains to be determined. However, important questions include whether tumors with HF-MSI require chemotherapy and whether they would respond to chemotherapy in the same way as other colorectal tumors. ❖

The Effect of Less Than Definitive Care on Breast Carcinoma: Recurrence and Mortality

ABSTRACT & COMMENTARY

Synopsis: *The care for patients with localized carcinoma of the breast is relatively standardized. Lash and colleagues have evaluated the outcomes of patients with localized carcinoma of the breast with respect to diagnostic and treatment parameters. Those patients who underwent less than definitive prognostic evaluations or treatment had significantly higher rates of breast cancer mortality.*

Source: Lash TL, et al. *Cancer* 2000;89:1739-1747.

Diagnostic evaluation and therapy in primary therapy for patients with early stage breast carcinoma have been recently well characterized.[1] In this study, a standard definitive diagnostic/prognostic evaluation

was considered to include an axillary dissection and evaluation of estrogen receptor status. Definitive primary therapy was defined as either a mastectomy or breast conserving surgery plus radiation therapy starting within five months of surgery. Definitive therapy for women with regional disease also included systemic adjuvant chemotherapy (with either CMF or cyclophosphamide and doxorubicin) and/or hormonal therapy with tamoxifen administered for five years. Women receiving definitive diagnostic/prognostic evaluation and definitive therapy were considered as a reference group (i.e. those women who received "definitive care"). The analyses were adjusted for the age of the patient at the time of diagnosis, the extent of disease, and the number or comorbid diseases.

Four hundred ninety-four female breast cancer patients were diagnosed at eight Rhode Island hospitals between July 1984 and February 1986. Re-identification of patients for outcome was performed through a cancer registry and 431 (87%) of these patients were identified. Of the 431 patients, 390 had local or regional disease and formed the basis of this report. Ninety-seven percent of the patients studied were white. One hundred sixty-four (68%) of the patients received definitive treatment for their local disease, and 130 (89%) patients received definitive therapy for regional disease. Patients with less than definitive prognostic evaluation for primary disease included patients who did not have an estrogen receptor evaluation (16%), an axillary dissection (12%), or neither (3%). For patients with regional disease, 6% did not have estrogen receptor evaluation and 5% did not have an axillary dissection. From a therapeutic standpoint, 60% of the women were considered to have had definitive therapy for their disease. The major causes for less than definitive therapy was the failure to implement systemic adjuvant therapy for regional disease (69 patients, 18% of the total) and the use of breast-conserving surgery without radiation (25 patients, 6% of the total). Women whose prognostic evaluation was less than definitive had a greater risk for breast cancer recurrence (hazard ratio 1.7, 95% confidence interval [CI], 1.0-2.7) and breast caner mortality (hazard ratio 2.2, 95% CI, 1.2-3.9) for events that occurred during the first five years of follow-up. Patients with less than definitive therapy had respective hazard ratios for these parameters of 1.6 (95% CI, 1.0-2.6) and 1.7 (CI, 1.0-2.8). Interestingly, events that occurred after more than five years of follow-up were not significantly different for the two groups.

COMMENT BY MICHAEL J. HAWKINS, MD

This is an interesting report that evaluates breast cancer recurrence and mortality with respect to adherence to well-accepted standards of medical care. While the reasons that women may not have received what was defined as definitive diagnostic or therapeutic care may vary, the differences identified in this study are striking. In addition, the analyses were not affected by age at diagnosis, stage of disease, or the presence of comorbid conditions. With greater access to nonreviewed literature via the internet, the number of patients who resist receiving treatment according to standard, evidence-based practice guidelines is increasing. These patients should be cautioned that deviations from standard care may be associated with a significantly increased (approximately 2-fold) risk for tumor recurrence and death from breast cancer. ❖

Reference

1. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. *CMAJ* 1998;158(Suppl 3):S1-83.

Host Defense and Survival in Lung Cancer

ABSTRACT & COMMENTARY

Synopsis: *Certain pathologic changes associated with a host immune response correlate with survival in lung cancer patients. Lymphocytic infiltration of the primary tumor and a cellular response in the regional nodes will predict outcome.*

Source: Di Giorgio A, et al. *Cancer* 2000;89:2038-2045.

If you believe that adjuvant therapy in lung cancer has potential benefits, how do you select eligible patients? Most oncologists consider factors such as the patient's age and the tumor's stage and grade. Although no method of selecting patients has emerged for which adjuvant therapy has proven to be effective, the retrospective analysis by Di Giorgio and associates looks at unique risk factors that might ultimately better define which patients are at high risk for recurrence.

The study by Di Giorgio et al was designed to evaluate whether the pathologic detection of an anticancer immune response in lung cancer specimens correlated with the clinical outcome. One hundred seventy-two patients with resectable lung cancer who survived beyond the postoperative period were selected from more than 3000 cases of lung carcinoma treated at the University of Rome from 1960 to 1997. Slides from at

least eight lymph nodes were required for each eligible patient.

From these 172 patients, Di Giorgio et al retrieved the slides of 2064 lymph nodes (mean 12, range 8-27). These regional lymph nodes were assessed for sinus histiocytosis (SH), paracortical lymphoid cell hyperplasia (PLCH) or follicular hyperplasia of the cortical area (FHCA). Sinus histiocytosis and PLCH were considered to be indicators of an antitumor cell-mediated immune response, whereas FHCA was considered to be evidence for an antibody-mediated response. The primary tumors were also assessed for lymphocytic infiltration, a surrogate marker of a local immune response.

Using methods described in the paper, patients were divided into four "immunomorphologic" groups: predominantly cellular immune response (20%), predominantly humoral immune response (11%), both cellular and humoral response (34%), and no evident immune response (35%). These subtypes showed no statistical correlation with gender, stage, or cell type. Of interest, however, was the relationship between survival and the immune response category.

Patients with a strong cellular immune response in the lymph nodes had the highest 10-year survival rate (about 60%), whereas those with a humoral response or no immune response at all had the worst 10-year survival (< 5%). An intermediate survival curve was seen for patients with both a cellular and humoral immune response (about 25%). A marked degree of lymphocytic infiltration in the primary tumor (rather than the lymph nodes) was also associated with an improved survival. In fact, a Cox regression analysis, which included the stage and histologic subtype, identified only lymphocytic infiltration of the primary tumor and the "immunomorphologic" pattern of the locoregional nodes as the most reliable independent variables for predicting survival after curative surgery for lung cancer.

COMMENT BY KENNETH W. KOTZ, MD

Using predefined patterns of an immune response, Di Giorgio et al found evidence of an active host defense in the regional lymph nodes in 64.5% of patients and in the primary tumor in 36.6% of patients. Older patients tended to have less immunoreactivity, but this did not reach statistical significance. The patients with small cell lung cancer tended to have less immunoreactivity than patients with non-small cell lung cancer, but for those patients who did react, the proportion of cellular and humoral responses was the same.

The most striking finding is the relationship between survival and the type of immune response in the regional nodes. To repeat, the highest survival was for patients with a cellular response. The addition of a humoral response worsened survival, and a humoral response alone was as bad as no response at all. Di Giorgio et al hypothesize that a cellular response prevents lymph node metastases, whereas a humoral response facilitates lymph node metastases. For example, the nodes of most node-negative tumors contained a predominantly cellular response whereas the nodes of most node-positive tumors contained mostly a humoral response.

The exact mechanism behind these observations is unknown. Di Giorgio et al suggest that a humoral response (perhaps due to increasing tumor size and shedding of antigens) might block the cytotoxic action of T-cells. Obviously, the biology of metastasizing cancer cells is extremely complicated. However, it is hoped that retrospective analyses such as the one by Di Giorgio et al might eventually lead to better selection of high-risk lung cancer patients so that any benefit afforded by adjuvant therapy can be more easily demonstrated. ❖

Evaluation of PC-SPES in Prostate Cancer Patients

ABSTRACT & COMMENTARY

Synopsis: *A Phase II study of the herbal supplement PC-SPES was performed with 33 androgen-dependent prostate cancer (ADPCa) patients and 37 androgen-independent prostate cancer (AIPCa) patients. All of the ADPCa patients achieved a PSA decline of greater than 80%, with a median duration of this response being greater than 57 wk. Nineteen (54%) of 35 AIPCa patients had a PSA decline of greater than 50%, with a median time to PSA progression of 16 wk (range, 2-69+ wk). Additional measures of response to PC-SPES, including bone scan improvement and resolution of a bladder mass seen on pelvic CT, were reported. Severe toxicities included pulmonary embolism (n = 3) and allergic reactions (n = 3). PC-SPES has activity in the treatment of both ADPCa and AIPCa with acceptable toxicity. Comparative studies of PC-SPES with more conventional means of antigen deprivation merits consideration.*

Source: Small EJ, et al. *J Clin Oncol* 2000;18: 3595-3603.

Pc-spes is an herbal supplement that has been used as a complementary or alternative medical therapy by patients with prostate cancer.[1] Initial reports have

identified the estrogenic nature of PC-SPES, and clinical activity has been reported in a small number of prostate cancer patients.[1] Preclinical studies have identified antiproliferative effects of PC-SPES against prostate cancer cells.[2] Since PC-SPES has received wide use in the community, a Phase II study was designed to evaluate efficacy and toxicity of PC-SPES in a prospective controlled study for prostate cancer patients (ADPCa and AIPCa).

Small and colleagues report results of a Phase II study involving 33 patients with ADPCa and 37 patients with AIPCa who received treatment PC-SPES at a target dose of nine capsules daily. The patients received 320 mg capsules, 1 orally t.i.d. for one week. If there were no apparent adverse events, the dose was escalated to two capsules orally t.i.d. for one week. A further escalation to a maximal dose of three capsules orally t.i.d. was permitted if no apparent adverse events occurred. This final dose was determined empirically based on a regimen commonly used in the community. The median age of patients with ADPCa was 64 (range, 48-86) and the median age of patients with AIPCa was 68 (range, 43-89). Baseline Karnofsky performance status (KPS) of both groups of patients was excellent, with a median KPS of 100 in the ADPCa patients (range, 90-100) and a median KPS of 90 in the AIPCa patients (range, 70-100).

One hundred percent of the ADPCa patients receiving PC-SPES had a greater than 50% PSA decline, and 54% of the AIPCa patients had a PSA decline of more than 50%. Additional measures of antitumor response were available in some of the patients and included bone scan improvement (2 of 2 ADPCa patients and 2 of 25 AIPCa patients) and soft tissue response measured by CT scan (1 of 1 patient ADPCa patient and 0 of 1 AIPCa patient). Endocrine changes included a decrease in testosterone level to less that 50 ng/ml in 97% (31/32) of the ADPCa patients, and 100% of the evaluated ADPCa patients reported a libido decline with therapy (24/24), potency decline with therapy (15/15), and gynecomastia/gynecodynia (32/32).

Severe toxicities (grade 4) included three patients with pulmonary embolism, one patient with elevated triglycerides and one patient with renal failure (the renal failure was considered unrelated to PC-SPES). The following grade 3 toxicities also occurred: allergic reactions (1 patient; 1.4%), atrial arrhythmia (1 patient; 1.4%), congestive heart failure (2 patients; 2.9%), diarrhea (2 patients; 2.9%), hyperglycemia (1 patient; 1.4%), leg cramps (1 patient; 1.4%), elevation in AST/ALT (1 patient; 1.4%), and elevated triglycerides (1 patient; 1.4%). The episodes of congestive heart failure were considered unrelated to PC-SPES. Common grade 1 and 2 toxicities included leg cramps, diarrhea, elevated cholesterol, constipation, fatigue, hyperglycemia, nausea, and elevated triglycerides. Many patients experienced gynecomastia/gynecodynia. Overall, treatment with PC-SPES was considered reasonably well tolerated. The primary severe toxicities were thromboembolic events. The duration of PC-SPES treatment at the time of pulmonary embolism was seven months in two patients and two weeks in the third patient.

COMMENT BY MARK R. ALBERTINI, MD

Several complimentary and alternative medical therapies are being used by cancer patients.[3] While most of these treatments have unknown (if any) benefit, some may have antitumor properties. Thus, identification of potential antitumor properties of some of these treatments may be informative. In addition, some of these treatments may present medical risks that should be identified.[4] Small et al proceeded with this Phase II study of PC-SPES due to its widespread use in the community and due to preliminary preclinical and clinical results suggesting antitumor activity.

This small Phase II study demonstrates androgen deprivation and subsequent antitumor effects in patients with androgen-dependent prostate cancer receiving PC-SPES. However, alternate safe conventional therapies are currently available for these patients.[5] Small et al also report antitumor activity of PC-SPES for patients with androgen-independent prostate cancer. Since current therapies for these patients provide limited benefit,[6-7] additional evaluation appears reasonable. Comparative studies will be needed to determine the relative activity of PC-SPES as a second- or third-line treatment for patients with androgen-independent prostate cancer.

The dose and schedule used in this study was empiric and was based on a dose and schedule of PC-SPES commonly used in the community. Additional clinical evaluation, with attention to dose and schedule, may improve the therapeutic potential of this treatment. In addition, use of PC-SPES in combination with other therapies could be considered. The need for a careful evaluation of unconventional complementary treatments that patients are taking is also emphasized by this study. As patients on clinical studies may also be taking complementary medications, this information is essential to appropriately evaluate both antitumor effects and toxicities of novel agents being tested in clinical studies. ❖

References

1. DiPaola RS, et al. *N Engl J Med* 1998;339:785-791.

2. Kubota T, et al. *Prostate* 2000;42:163-171.
3. Eisenberg DM, et al. *N Engl J Med* 2000;328:246-252.
4. Angell M, Kassirer JP. *N Engl J Med* 1998;339: 839-841.
5. Eisenberger M, et al. *N Engl J Med* 1998;339: 1036-1042.
6. Small EJ, Vogelzang NJ. *J Clin Oncol* 1997;15: 382-388.
7. Smith DC, et al. *Urology* 1998;52:257-260.

CME Questions

1. **Palliative surgical options for patients with intractable pain from metastatic renal cell carcinoma to bone include:**
   a. amputation.
   b. wide local excision with limb sparing.
   c. marginal excision (curettage) with cryotherapy.
   d. All of the above

2. **In the study by Di Giorgio et al, which of the following is true?**
   a. Survival correlated with serum anti-tumor antibodies.
   b. Survival correlated with the administration of an autologous tumor vaccine.
   c. The presence of a cellular immune response was associated with an improved survival.
   d. The presence of a humoral immune response was associated with an improved survival.

3. **Which of the following is *false* concerning the presence of high-frequency microsatellite instability in colorectal cancer?**
   a. Tumors are more likely to be located proximally.
   b. Tumors are more likely to have a mucinous or medullary histologic pattern.
   c. Tumors are more likely to have an improved survival.
   d. Tumors are highly likely to overexpress p53.

4. **What was the risk of dying within five years of diagnosis for women who received less than standardized diagnostic procedures or treatment compared with those who did?**
   a. No difference
   b. Approximately twice that of women who received standard care
   c. Approximately 10 times that of women who received standard care
   d. Approximately 10% greater than that of women who received standard care

5. **Which of the following statements about tamoxifen use in patients with BRCA1 mutation is true?**
   a. Its use in the treatment of primary breast cancer will reduce the likelihood of a breast cancer occurring in the contralateral breast.
   b. Its use in the treatment of primary breast cancer will reduce the likelihood of ovarian cancer.
   c. Its use in the treatment of primary breast cancer will be more effective than chemotherapy in protecting the patient from breast cancer occurring in the contralateral breast.
   d. Its use in the treatment of bilateral breast cancer will reduce the occurrence of ovarian cancer.

6. **Which of the following statements is *false* about PC-SPES in patients with progressive prostate cancer?**
   a. PC-SPES has estrogenic activity.
   b. Severe toxicities of PC-SPES include thromboembolic events.
   c. Antitumor effects of PC-SPES are greater than those achieved with estrogen therapy.
   d. Libido decline occurred in 100% of patients with androgen-dependent prostate cancer receiving PC-SPES.

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Clinical Oncology Alert*. Send your questions to: Robert Kimball, *Clinical Oncology Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Clinical Oncology Alert* via the internet by sending e-mail to robert.kimball@ahcpub.com. ❖

In Future Issues:

High-Dose Chemotherapy for Aplastic Anemia