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Tamoxifen Cuts the Risk of Breast Cancer in Half

ABSTRACT & COMMENTARY

One of the interesting secondary outcomes of the careful clinical studies conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and other multicenter groups through the years has been the observation that women with breast cancer who took adjuvant therapy with tamoxifen not only had a significantly lower rate of disease recurrence but, in addition, had a significantly lower risk of developing cancer in the contralateral breast.[1-4] Because women who have had breast cancer are at high risk of developing a second breast cancer, this secondary benefit from tamoxifen adjuvant therapy led to the notion that perhaps tamoxifen would be capable of influencing the risk of developing breast cancer in other high-risk groups. Tamoxifen has also been shown to have beneficial effects on the risk of cardiovascular disease, the development of osteoporosis, and possibly even the occurrence of dementia and Alzheimer's disease. Balanced against these substantial potential benefits was a small risk of developing estrogen-related complications, such as thromboembolic disease and endometrial cancer, because of the weakly estrogenic effects of tamoxifen.

In light of these considerations, NSABP implemented a randomized clinical trial (NSABP-P1) to examine whether tamoxifen could significantly lower the risk of developing breast cancer in a group of women considered to be at increased risk. Eligibility criteria included the following: age 60 years or older; age 35-59 years with a calculated five-year risk of 1.66% (note that the Breast Cancer Risk Assessment Tool used to calculate the risk [based upon the model of Gail et al[5]] is now available as an interactive computer program through the National Cancer Institute's Cancer Information Service at 1-800-4-CANCER or online at http://cancertrials.nci.nih.gov) or a history of lobular carcinoma in situ; a life expectancy of at least 10 years; a negative breast examination and mammagram within the past six months; and no history of thromboembolic disease or deep venous thrombosis. Women with an intact uterus had an endometrial tissue sampling before starting treatment. Primary outcome measures were the rate of development of breast cancer. Secondary outcome measures were the incidence of myocardial infarctions and the incidence of osteoporotic bone fractures.

From April 1992 through May 1997, 13,388 women (of 98,018 undergoing risk assessment) were randomly assigned to receive either tamoxifen 20 mg/d or oral, daily placebo for five years. The trial was a double-blind, placebo-controlled design; 6707 received placebo and 6681 received tamoxifen. Twenty-one percent of women stopped their assigned therapy prematurely—19.7% in the placebo group and 23.7% in the tamoxifen group. Complete follow-up was available on 92.4% of the participants.

In total, 368 invasive and noninvasive breast cancers developed among the 13,175 patients with follow-up, 244 on placebo, 123 on tamoxifen. Of these, 175 cases of those on placebo were invasive and 89 cases on tamoxifen were invasive ($P < 0.00001$ in favor of tamoxifen). The cumulative incidence through 69 months was 43.4 per 1000 women in the placebo group and 22 per 1000 women in the tamoxifen group. Thus, tamoxifen significantly reduced the risk of both invasive and noninvasive breast cancer. Significantly reduced risk was seen in women of all ages: younger than 49, 44% risk reduction (RR); 50-59, 51% RR, and older than 60, 55% RR. Risk was reduced in women with a history of lobular carcinoma in situ (56%) or atypical hyperplasia (86%). Significantly reduced risks were observed in all risk categories.

Tamoxifen-treated patients did not have a reduced risk of myocardial infarction, but this may be related to the length of follow-up. Bone fractures were significantly reduced in the tamoxifen arm. Endometrial cancer occurred with increased incidence on the tamoxifen arm: 36 cases (13/1000 women) vs. 16 cases (5.4/1000 women) on the placebo arm. All the cancers on the tamoxifen arm were FIGO stage I. More women who received tamoxifen developed deep vein thrombosis (35 vs 22) and pulmonary embolus (18 vs 6). The incidence of strokes and cataracts was not significantly different on the two arms. (Fisher B, et al. *J Natl Cancer Inst* 1998;90:1371-1388.)

COMMENTARY

Well, it's hard to imagine news much better than this. The use of tamoxifen reduces a woman's risk of developing breast cancer by about 50%. A bonus from the treatment is a reduction in osteoporosis and the morbidity associated with fractures. At this particular time of follow-up, tamoxifen has not yet shown a beneficial effect on deaths from heart disease, but only a small fraction of patients have died so far. This study did not assess cognitive endpoints, but it is also possible that tamoxifen-treated patients will have less age-related cognitive impairment.

With these documented and not-yet-documented gains come some downside risks. The risks of thromboembolic disease and endometrial cancer are somewhat increased by taking tamoxifen. However, the balance of risk and benefit is overwhelmingly in favor of benefit. The subset of patients with genetic mutations that increase their risk has not yet been examined; however, blood samples are available to determine BRCA1 and BRCA2 phenotypes and such correlations will be made in future analyses. In addition, given the broad efficacy of tamoxifen in diverse risk groups, the question must be asked about how high the risk must be before the risk-benefit ratio is favorable. Modifications of the existing algorithms are currently being made to help with these decisions.

Furthermore, we may not yet have gotten all the benefit that is possible to obtain from tamoxifen use. The question remains open whether longer duration of tamoxifen treatment would exert greater benefits. In addition, it is not yet clear whether the newer selective estrogen receptor modulators (SERMs), such as raloxifene, will have different or greater effects than tamoxifen. Ongoing studies, including NSABP-P2, are addressing this question. The success of this study makes interpretation of other ongoing studies somewhat complicated. In my opinion, it is no longer appropriate to include a placebo arm in breast cancer prevention studies. The new SERMs need to be demonstrated to be superior to tamoxifen rather than placebo. Primary care physicians should develop a level of comfort using the

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

GROUP PUBLISHER: Donald R. Johnston.
EXECUTIVE EDITOR: Glen Harris.
ASSISTANT MANAGING EDITOR: Robin Mason.
COPY EDITOR: Neill Larmore.
MARKETING MANAGER: Debra Zelnio.

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: $21.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421

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

Editorial E-Mail Address: neill.larmore@medec.com

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

Subscription Prices

United States
$189 per year (Student/Resident rate: $95).

Multiple Copies
1-9 additional copies: $95 each; 10 or more copies: $57 each.

Canada
$219 per year plus GST (Student/Resident rate: $110 plus GST).

Elsewhere
$219 per year (Student/Resident rate: $110).

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Please call Robin Mason, Assistant Managing Editor, at (404) 262-5517 or Neill Larmore, Copy Editor, at (404) 262-5480 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

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risk assessment tool and applying it to individual patients. If an individual is found to be at increased risk of breast cancer, the first choice would be to enter the patient on a prospective randomized trial. If that is not possible, women should be informed of the risks and benefits of tamoxifen use and be permitted to obtain the benefits proven in this landmark study. ❖

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Taking Colorectal Cancer Surgery to the Next Level: Resecting Pulmonary and Hepatic Metastases

ABSTRACT & COMMENTARY

Synopsis: *In this series of 30 patients from Japan in whom primary, curative-intent surgery was followed by the development of metastases in both the liver and the lung, a surgical approach to these metastatic lesions was undertaken. Surgical morbidity was low and there were no surgical deaths. Survival was 30 months (range, 7-108 months) after metastatic disease resection and 48.5 months (range, 11-149 months) after excision of the primary colorectal tumor. These results compare favorably with other treatment modalities for metastatic colorectal cancer.*

Source: Murata S, et al. *Cancer* 1998;83:1086-1093.

Approximately 40% of patients who undergo curative intent surgery for colorectal cancer will succumb to metastatic disease. The gradual drop in this percentage is the result of new and more aggressive surgical techniques and the aggressive use of adjuvant chemotherapy.[1] However, when metastatic disease is recognized, long-term survival is uncommon, and this is especially true when the metastatic disease involves more than one site (e.g., liver and lung). In this series from the National Cancer Center Hospital in Tokyo, data from 30 patients who had undergone resection of both hepatic and pulmonary metastases from either colon (n = 15) or rectal (n = 15) cancer were evaluated.

The selection criteria for resection of hepatic and/or pulmonary metastases included original curative intent surgery (including patients who presented with hepatic metastases) and an assessment that additional resection would be well-tolerated. After original surgery, patients were followed carefully and were considered candidates when either hepatic or pulmonary (or both) metastases were recognized.

Thus, this was a series of 30 patients who were treated surgically for both hepatic and pulmonary metastases. All operations were well-tolerated and there were no surgical deaths. Median survival times were 30 months (range, 7-108 months) after resection of both hepatic and pulmonary metastases and 48.5 months (range, 11-149 months) after excision of the primary colorectal tumor. Actuarial one-, three-, and five-year survival after resection of both hepatic and pulmonary metastases was 86.7%, 49.3%, and 43.8%, respectively.

Murata and colleagues conclude that resection of metastatic disease may prove useful in prolonging the survival for selected patients with metastatic disease involving the liver and lungs.

COMMENTARY

It is difficult to find fault with Murata et al's conclusions based upon the data presented. Granted, this was a non-randomized, descriptive report from a single institution, but it did not appear that patients were selected for any parameter that would favor optimal clinical outcomes. Thus, patients as old as 81 years were included, as were those with short disease-free intervals (< 1 year) after primary surgery. In fact, using a multivariate analysis, only two features independently influenced survival. These were the time of appearance of metastasis (patients with simultaneous liver and lung metastases fared worse than those with serial occurrences and operations) and patients with unilateral pulmonary metastases survived longer than those with bilateral disease. Of interest, age, disease-free interval, and the site of primary tumor were not significant independent factors.

This is an intriguing series. Recently, there has been increased enthusiasm for a surgical approach to hepatic metastases from previously resected colon cancers.[2] Like axillary node metastases from primary breast cancers, the liver has been considered a regional site for metastatic disease and, hence, the rationale for curative intent resection. The appearance of pulmonary metastases has other biological implications, indicating the entrance of tumor cells into the systemic circulation.

The survival data presented in this report compare favorably with the results observed in similarly staged patients receiving chemotherapy. Morbidity was minimal and mortality was non-existent. This, too, compares favorably with chemotherapy. In fact, in this series of 30 patients, all of whom had both hepatic and pulmonary metastases, only eight received chemotherapy. This is a fresh look at the management of metastatic disease and the results warrant further investigation. ❖

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Testicular Atrophy and the Aggressiveness of Prostate Cancer

ABSTRACT & COMMENTARY

Synopsis: *Assessment of testicular histology was undertaken in 78 patients who had therapeutic orchiectomy for advanced prostate cancer. Among 35 patients who had orchiectomy for progressive disease after primary radiation therapy to the prostate bed, 25 had prominent testicular atrophy and the stage and grade of their original prostate tumors were higher. Survival was worse when compared to the 10 who did not have prominent testicular atrophy. Similarly, of the 25 men who presented with advanced (Stage D2) disease and were treated by orchiectomy, the seven who were found to have prominent testicular atrophy had shorter survival when compared to the 18 without prominent atrophy. Thus, the presence of prominent testicular atrophy at the time of therapeutic orchiectomy identifies a subset of patients with more aggressive disease and worse prognosis.*

Source: Danniell HW. *Cancer* 1998;83:1170-1173.

Orchiectomy is a commonly prescribed surgical intervention for men with prostate cancer who have recurrence after local excision or radiation or who present with metastatic disease. Whereas this usually results in gratifying (albeit temporary) tumor regression in the great majority of patients, there is significant variability, and, in some patients, there is no response. In a series of patients who underwent orchiectomy for prostate cancer, the degree of testicular atrophy was determined by histological analysis and correlated with prostate cancer grade and patient survival.

Thirty-five patients had orchiectomy after progression from primary radiation to the prostate bed. Of these, 25 had testicular atrophy, and those with atrophy had worse five-year, tumor-specific, post-orchiectomy survival when compared to the 10 men without testicular atrophy (30% vs 89%; P = 0.02). Furthermore, a review of the original tumor histology in these patients indicated that these 25 men had tumors of more advanced stage and with higher histological (Gleason) grade.

Included in the series were 25 patients who had not received prior radiation but presented with advanced (Stage D2) disease and had orchiectomy as primary therapy. Seven of these men had prominent testicular atrophy, and they, too, had more undifferentiated prostate cancer histopathology and shorter survival when compared to the 18 patients without testicular atrophy. For this group, tumor-specific, post-orchiectomy survival at two years was 43% for those with prominent atrophy compared to 72% for those without.

There were an additional 18 patients who underwent orchiectomy for non-Stage-D2 disease and had not received prior radiation therapy. Of these, five had prominent atrophy and 13 did not. For this subset, there was no difference in survival after orchiectomy, with a total of only three deaths during the study period.

Danniell concludes that the demonstration of testicular atrophy at the time of therapeutic orchiectomy for prostate cancer is associated with poor post-orchiectomy prognosis.

COMMENTARY

In these days of molecular/genetic probing for prognostic factors, it is easy to overlook the obvious. Indeed, if Danniell had found that the over-expression of a certain gene correlated as strongly with survival as did the presence of prominent testicular atrophy, the paper might have elicited a swell of excitement. It might be argued that under that circumstance, the genetic marker might lead to an increased understanding of the pathogenesis of the disease. Yet, the same could be said about this paper.

It has been known for some time that low serum testosterone levels portend a worse prognosis for patients in whom hormone ablation therapy is to be undertaken.[1-3] It stands to reason that if the tumor has developed in an androgen-depleted state, it is less likely to be androgen-dependent and, therefore, is more likely to demonstrate autonomous hormone-independent growth and be more aggressive. Although not reported in this series, it is likely that testicular atrophy would be associated with low serum testosterone levels.

Testicular histology at the time of therapeutic orchiectomy might prove to be a useful (and inexpensive) clinical tool in assessing the likelihood of sustained response to hormonal ablation. With the advent of effective palliative chemotherapy for prostate cancer patients who have progressed after hormonal ablation,[4] perhaps those with prominent testicular atrophy at the time of orchiectomy could be considered candidates for alternative, adjunctive approaches as well. ❖

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Reinduction of Androgen-Responsiveness in Prostate Cancer: The Role of Caveolin

BASIC SCIENCE WITH CLINICAL APPLICATION

Synopsis: *Hormone-independent human prostate cancer cells usually express increased levels of a protein called caveolin, a major component of caveolae, cave-like structures involved in membrane trafficking and import of molecules into the cell. Decreasing the level of expression of caveolin experimentally with an antisense vector resulted in a return of hormone-responsiveness. It is possible that a therapeutic intervention that was capable of interfering with caveolin expression could restore hormone sensitivity in advanced prostate cancer.*

Source: Nasu Y, et al. *Nature Med* 1998;4:1062-1064.

The progression of prostate cancer coincides with a change in the influence of androgens on tumor growth. Early in the course of disease, prostate cancer is dependent on androgen for survival. Without androgen, prostate cancer cells undergo apoptosis. Clinical treatment approaches take advantage of this hormone dependence. Following primary treatment (surgery or radiation therapy), men with disease spread beyond the prostate gland typically receive either medical or surgical castration and the majority of patients experience some objective benefit from androgen deprivation. Over time, however, the prostate cancer acquires additional genetic defects and becomes more abnormal in its cytologic appearance. And, among the most important clinical markers of disease progression is the development of hormone-independent prostate cancer.

The nature of the changes in the cells that accompany hormone independence is slowly being elucidated. For example, it appears that the antiapoptotic protein bcl-2 is overexpressed primarily in hormone-independent prostate cancer and is virtually undetectable in hormone-dependent prostate cancer,[1] and consequently, the hormone-independent cells are relatively refractory to apoptosis. Bcl-2 overexpression also contributes to drug resistance.

An approach to understanding tumor progression (and other differences between cell types) that is beginning to bear unexpected fruit is an experimental procedure called differential display. In this method, messenger RNA from two (or more) cell lines with different phenotypic characteristics is first expanded and then compared by running the nucleic acids on a polyacrylamide gel. If one examines cells that are similar, except for a particularly easily identifiable feature, the two cell lines will have some messages in common and some that are expressed distinctively in one or the other. Bands can be cut out of the gel and sequenced using micro-methods, and, in this fashion, genes can be identified that are "differentially expressed," that is, expressed in one cell but not the other. When such an approach was taken to examine hormone-dependent and hormone-independent prostate cancer cell lines, Yang and colleagues identified caveolin as a gene overexpressed in hormone-independent cells.[2]

Caveolin is the major protein component of cell structures located near the cell membrane called caveolae or little caves. Caveolae are one of at least three forms of coated vesicles, regions of the cell membrane with characteristic proteins associated with them that face the cytosol. They form a unique endocytic and exocytic compartment at the surface of most cells and are capable of importing molecules and delivering them to specific locations within the cell, exporting molecules to extracellular space, and compartmentalizing a variety of signaling activities. Caveolins form a scaffold onto which many signaling molecules can assemble to generate multi-component signaling complexes. In addition to concentrating these signal transducers within a distinct region of the plasma membrane, caveolin binding may functionally regulate the caveolae-associated signaling molecules. The best evidence is that caveolin most often inhibits signal transduction.

Androgen-independent prostate cancer cells are usually not androgen-independent because they fail to express androgen receptors. Indeed, amounts of androgen receptor are often increased in hormone-unresponsive prostate cancer cells. Given that caveolin expression

increases in hormone-independent prostate cancer cells and, paradoxically, the androgen receptor gene undergoes amplification and increased expression in most prostate cancers, it is reasonable to ask whether these two findings are related. Is the caveolin expression interfering with the function of the androgen receptor?

Nasu and colleagues examined the relationship by interfering with caveolin expression in hormone-independent mouse and human prostate cancer cells using an antisense construct stably expressed by infecting tumor cells with adenovirus containing the construct. When caveolin levels decreased in the cells, sensitivity to androgen withdrawal returned. In vivo, cells with lower levels of caveolin had much slower rates of tumor progression than did cells expressing large amounts of caveolin. And, when antisense-containing clones were selected for androgen resistance in vivo, they uniformly were overexpressing caveolin. Conversely, when androgen-sensitive cells were made to express caveolin through adenovirus-mediated infection, the cells became androgen insensitive.

Thus, the correlation appears direct. Prostate cancer cells may undergo a variety of changes in the course of progressing from androgen-sensitive to androgen-insensitive. However, this process appears to depend in a crucial way on the increased expression of caveolin. Many important and interesting experiments are needed to follow up on these interesting findings. Does increased caveolin mean increased numbers of caveolae? Is the androgen receptor associated with caveolae or are the effects of caveolin indirect, or perhaps even caveolae-independent? Does caveolin form a complex with the androgen receptor? Does caveolin bind to other molecules in an androgen signaling cascade?

However, the most clinically relevant application of this important work is the need for therapeutic agents capable of inhibiting the expression of caveolin. It is hoped that blocking the expression of caveolin does not result in some horrific toxicity, a possibility that is of great concern in light of the ubiquitous nature of caveolae and the as yet uncertain dependence of the caveolae on caveolin for their function. Thus, in addition to the developmental therapeutic approaches that aim to overcome bcl-2 expression and to interfere with other genetic lesions that characterize prostate cancer, it is also relevant to consider caveolin antagonists as being a high priority for drug discovery. ❖

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Perugia Consensus Conference: Guidelines on Chemotherapy- and Radiation Therapy-Induced Emesis

CLINICAL REVIEW

Synopsis: *Cancer treatments can be grouped on the basis of emetogenic effects into highly emetogenic, moderate-high, low-moderate, and low. Emesis can be acute (occurring within 24 hours of treatment), delayed (occurring between day 2 and day 7 after treatment), or anticipatory (occurring before treatment). Anticipatory emesis is best prevented by effectively managing acute and delayed emesis. Emesis prevention has become significantly more likely because of the introduction of serotonin receptor type 3 (5-HT) antagonists and their use in combination with dexamethasone.*

Source: Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer. *Ann Oncol* 1998;9:811-819.

Treatment-induced nausea and vomiting are some of the most common and distressing side effects of cancer treatment. In some instances, the desire to avoid this complication may make a patient refuse treatment with the potential to prolong survival. Much is known about the mechanisms of treatment-induced emesis, but the ability to intervene and prevent this problem has been considerably improved with the introduction of serotonin (5-hydroxytryptamine or 5-HT) receptor type 3 antagonists, such as ondansetron, granisetron, tropisetron, and dolasetron. The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC) held a consensus conference in Perugia, April 28-29, 1997, and produced consensus documents regarding eight areas of interest. These documents have been published in full in the journal of the MASCC called *Supportive Care in Cancer*.[1]

Table 1 groups cancer treatments by emetogenic potential. (*See Table 1.*) This effort is, of course, flawed because emesis can be influenced by a variety of factors, including those related to the treatment (other agents being given, dose, schedule, etc.) and those related to the patient (primary tumor, sites of involvement, age, sex, propensity to develop motion sickness, and others).

Table 1

Emetogenic potential of chemotherapeutic agents

Degree of Emetogenic Potential	Agents
High	cisplatin > 50 mg/m^2, mechlorethamine streptozocin, dacarbazine cyclophosphamide > 1500 mg/m^2 carmustine >250 mg/m^2
Moderate-high	cisplatin < 50 mg/m^2, cytarabine > 1 g/m^2 carboplatin, ifosfamide, doxorubicin carmustine < 250 mg/m^2, epirubicin cyclophosphamide < 1500 mg/m^2 epirubicin, topotecan, irinotecan procarbazine, mitoxantrone methotrexate > 250 mg/m^2
Low-moderate	docetaxel, paclitaxel, etoposide methotrexate > 50 or < 250 mg/m^2 mitomycin C, gemcitabine fluorouracil < 1000 mg/m^2
Low	bleomycin, busulfan, chlorambucil cladribine, fludarabine, hydroxyurea melphalan, methotrexate < 50 mg/m^2 6-thioguanine, vinblastine, vincristine vinorelbine

A large number of controlled trials have been performed in chemotherapy-induced emesis, a fact that has made it difficult to keep up with the literature. However, a few general principles have emerged from these studies and they are summarized in Table 2. Certainly, a 5-HT antagonist plus dexamethasone has become the prevention of choice for highly emetogenic chemotherapy. Complete protection against vomiting has been documented in 70-90% of patients treated with this combination.[2] It appears that the oral route of administration is just as effective as intravenous administration.[3] The combination prevention regimens that include 5-HT antagonists are probably more effective and are certainly less toxic than regimens including metoclopramide. The addition of a dopamine antagonist (metopimazine) to a 5-HT antagonist appears to increase the antiemetic efficacy, but additional randomized studies are needed.[4]

The optimal 5-HT antagonist has not been determined. Some pharmacologic differences have been described, but, in general, their efficacy and tolerability are comparable. Data are conflicting about equivalent doses of the agents. In the United States, the most commonly used single IV dose of ondansetron is 32 mg or about 0.45 mg/kg. This is four times higher than the most commonly used single IV dose of ondansetron (8 mg) in Europe. By contrast, the single agent dose of granisetron is higher in Europe than in the United States (3 mg vs 1 mg). Table 3 lists the recommended doses for the individual 5-HT antagonists in the setting of highly emetogenic and moderate-high emetogenic agents. Decisions about use are mainly based on convenience of use and cost.

Table 2

Recommendations for specific clinical settings

Clinical Problems	Consensus Treatment of Choice
Single high-dose cisplatin	
Acute emesis	5-HT antagonist + dexamethasone
Delayed emesis	dexamethasone + metoclopramide or 5-HT antagonist
Single dose of moderate-high agents	
Acute emesis	5-HT antagonist + dexamethasone
Delayed emesis	dexamethasone and/or 5-HT antagonist
Cisplatin at low doses daily	5-HT antagonist + dexamethasone daily
Oral CMF	dexamethasone + metoclopramide or 5-HT antagonist
Refractory emesis in patients failing prophylaxis	5-HT antagonist + dexamethasone + metopimazine
Anticipatory emesis	Alprazolam Behavioral therapy (hypnosis, etc.)
High-dose chemotherapy	5-HT antagonist ± dexamethasone
Radiation therapy	
Highly emetogenic	5-HT antagonist ± dexamethasone
Moderately emetogenic	5-HT antagonist
Emetogenic therapy in children	5-HT antagonist + dexamethasone

Anticipatory nausea occurs in up to 20% of patients but is mainly a problem for patients in whom emesis prevention therapy was ineffective and resulted in frequent or severe nausea and vomiting. The use of low-dose alprazolam (0.5-2 mg) taken daily significantly reduced the incidence of anticipatory nausea and vomiting from 18% to 0% in one prospective, randomized, double-blind placebo-controlled study.[5] But, the effects may not last through prolonged courses of chemotherapy. Behavioral interventions, such as desensitization and hypnosis, have also been shown to be beneficial in some instances.

Table 3

Dosage and schedule of 5-HT antagonists

Agent	Dose and Schedule for Highly Emetogenic Agents	Dose and Schedule for Moderately-High Agents
Ondansetron	8 mg single IV dose 24 mg single oral dose	4-8 mg PO tid or bid
Granisetron	10 mcg/kg single IV dose 2 mg single oral dose	2 mg PO qd or bid
Tropisetron	5 mg single IV dose	insufficient data
Dolasetron	1.8 mg/kg single IV dose 200 mg single oral dose	100-200 mg PO qd

Antiemetic prophylaxis, together with the prevention of infectious death during treatment-induced granulocytopenia, is among the most impressive advances in cancer treatment. Despite the progress in prevention, numerous areas remain insufficiently researched to provide guidelines for management of proven value. For example, the rescue of patients in whom prophylaxis fails remains a difficult problem. New agents in development (for example, neurokinin inhibitors)[6] may make antiemetic therapy even more effective and relegate concerns about this important complication to the trash heap of issues no longer justifying any concern when choosing cancer treatment. ❖

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CME Questions

18. Which of the following statements is true regarding women at increased risk of breast cancer?

a. Tamoxifen use daily for 10 years significantly reduces the risk of breast cancer.
b. Tamoxifen use daily for two years significantly reduces the risk of breast cancer.
c. Tamoxifen use daily for five years significantly reduces the risk of breast cancer.
d. The beneficial effects of tamoxifen on breast cancer risk are outweighed by toxicities associated with tamoxifen use.
e. Tamoxifen and raloxifene are equally effective in the prevention of breast cancer.

19. Which of the following statements about testicular histology in patients with prostate cancer is true?

a. Prominent testicular atrophy is associated with a worse prognosis for patients with advanced disease whether they have received prior radiation therapy.
b. Prominent testicular atrophy is associated with a better prognosis for patients with advanced disease, whether they have received prior radiation therapy.
c. Prominent testicular atrophy is associated with a worse prognosis for patients who present with Stage D2 prostate cancer, but not for patients who have relapsed after prior radiation therapy or surgery.
d. There is no association of testicular atrophy and prostate cancer prognosis.
e. Testicular atrophy reflects chronic androgen excess.

Annual Statement of Ownership, Management, and Circulation

UNITED STATES POSTAL SERVICE

Statement of Ownership, Management, and Circulation
(Required by 39 U.S.C. 3685)

1. Publication Title	2. Publication No.	3. Filing Date
Clinical Oncology Alert	0 8 8 6 - 7 1 8 6	9/25/98
4. Issue Frequency	**5. No. of Issues Published Annually**	**6. Annual Subscription Price**
Monthly	12	$199.00

7. Complete Mailing Address of Known Office of Publication *(Street, City, County, State, and ZIP+4) (Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Name: Willie Redmond

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305 — Telephone Number: 404/262-5448

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*: Don Johnston, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*: Suzanne Zunic, same as above

Managing Editor *(Name and Complete Mailing Address)*: Miriam Timmerman, same as above

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13. Publication Name: Clinical Oncology Alert — 14. Issue Date for Circulation Data Below: September 1998

15. Extent and Nature of Circulation	Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
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g. Total Distribution *(Sum of 15c and 15f)*	1883	1916
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