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New Directions in Breast Cancer Research and Therapeutics

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I. CRAIG HENDERSON, MD, GUEST EDITORS

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**Preface**  
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*Advances in Breast Cancer Research*  

**Clinical Relevance of Breast Cancer Biology**  
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Biological properties of breast cancer are reviewed in relation to their ability to provide information about etiology, prognosis, or response to therapy. The authors suggest guidelines for the rigorous and systematic evaluation of biologic factors in relation to the prognosis and treatment of breast cancer.  

**The Genetics of Breast Cancer**  
Briggs W. Morrison  
Some of the genetic abnormalities that give rise to human breast cancer have been identified. This article reviews the biology of the oncogenes c-myc and neu and the antioncogene p53. Data supporting the role of these genes in the pathogenesis of human breast cancer are reviewed. Potential diagnostic and therapeutic applications that have developed out of our understanding of the molecular genetics of breast cancer are also discussed.  

**Growth Factors and Their Receptors**  
Debasish Tripathy and Christopher Benz  
Breast cancer represents a type of malignancy that is amenable to therapy targeting growth factors and receptors. There is consid-
erable evidence that signaling mechanisms involving growth factors and their receptors are important in the normal development of breast epithelium. Dysregulation of these pathways may contribute to the proliferative, invasive, and metastatic phenotypes of breast cancer cells in humans. Approaches being tested in the preclinical setting include antibodies or peptides that disrupt receptor-ligand interactions as well as other compounds that can interfere with downstream signalling.

Angiogenesis and Breast Cancer
Daniel F. Hayes

Preclinical studies have established an association between angiogenesis and the oncogenic process for many malignancies. Recent studies have suggested that the presence of neovascularization in primary breast cancer tissues is correlated with a high risk of distant metastases and mortality. Several angiogenic factors have been identified. At least one of these, basic fibroblast growth factor (bFGF), can be monitored in human serum and urine, and preliminary studies suggest that circulating bFGF levels are elevated in patients with breast cancer.

Overview of the Biologic Markers of Breast Cancer
Kathleen Porter-Jordan and Marc E. Lippman

The prognostic potential of several of the newer biological markers of breast cancer are discussed, with emphasis on markers of tumor growth, invasion, and tumorigenesis. Reviewed are data supporting possible use of ErbB-2 to predict for improved response to adriamycin, Hsp 27 to predict for failure of doxorubicin, and pS2 or EGFR to provide supplemental information predicting response to hormonal therapy.

Estrogen Receptor Molecular Biology
Myles Brown

Recent advances in estrogen receptor molecular biology and the dissection of its important functional and structural domains has led to a greater understanding of the factors underlying the hormone responsiveness of breast cancer. A coherent model for the partial agonist activity of tamoxifen has been developed. In addition, the potential mechanisms of tamoxifen resistance can now be explored at the molecular level. This has led to the development of pure antiestrogens that may be capable of clinical utility.

Advances in Therapeutics
New Directions for Breast Cancer Therapeutic Research
Michael A. Friedman

For the past two decades, attempts to improve chemotherapy for patients with breast cancer have emphasized the use of currently
available agents. Research by drug discovery programs of the National Cancer Institute has identified a number of clinically promising novel agents. Conceivably, within the next several years there could be a doubling of the chemotherapy armamentarium for breast cancer—more than 30 active cytotoxic agents.

**Paclitaxel (Taxol) in Breast Cancer**
Susan G. Arbuck, Andrew Dorr, and Michael A. Friedman

Paclitaxel (Taxol) is a diterpine plant compound that was isolated initially from the bark of the western yew tree, *Taxus brevifolia*, but can now be produced by semisynthesis from a renewable source. Paclitaxel is the first new agent in the past decade to have confirmed single agent activity in breast cancer in excess of 50%. A 28% response rate has been reported in doxorubicin-refractory patients. Ongoing studies include attempts to combine paclitaxel with other drugs used for breast cancer treatment and with radiation.

**Navelbine and the Anthrapyrazoles**
Alison L. Jones and Ian E. Smith

This article reviews the preclinical and early clinical development of navelbine and the anthrapyrazoles. The differences in structure from the “parent” compounds that may confer clinical advantages are discussed. The preclinical data, clinical pharmacology, and Phase I trials are reviewed. Further development of these drugs in Phase II trials and comparative studies is also discussed.

**Bisphosphonates in Breast Cancer Patients with Skeletal Metastases**
Charles L. Shapiro

The utility of bisphosphonates is well established in the treatment of acute hypercalcemia of malignancy. Bisphosphonates may also decrease the complications and morbidity of skeletal metastases. This article emphasizes the use of bisphosphonates in breast cancer patients with skeletal metastases.

**Clinical Controversies and Management Issues**

**Mammography in Women Under 50**
Anthony B. Miller

In this article, the evidence relating to the evaluation of effectiveness of early detection of breast cancer in women age 40 to 49 is reviewed, in light of the considerable controversy that has arisen over whether women in this age group should be given routine mammography screening. Of necessity, evidence is also provided on its effectiveness in older women, to facilitate comparison.
Hormone Replacement Therapy in Women with a History of Breast Carcinoma
Claudine J. D. Isaacs and Sandra Meta Swain

Hormone replacement therapy in women with a history of successfully treated breast cancer is felt to be contraindicated. Very little direct information is available regarding the effect of such therapy in this patient population. This article reviews the evidence both supporting and refuting a causative role for estrogen and progesterone in breast cancer. The majority of evidence supports such a role. The use of tamoxifen as an alternative treatment modality is examined.

A Practical View of Prognostic Factors for Staging, Adjuvant Treatment Planning, and as Baseline Studies for Possible Future Therapy
Peter M. Ravdin

Recent advances in the basic sciences have led to a number of mechanistically important molecules being identified and measured in normal and neoplastic breast tissue. Although new information has potential to improve prognostic assessment of breast cancer patients, inappropriate application can be fiscally irresponsible and decrease the accuracy in the prognostic assessment of breast cancer patients.

Adjuvant Therapy of Breast Cancer
Charles L. Shapiro and I. Craig Henderson

This article examines questions about adjuvant systemic therapy, especially in premenopausal and postmenopausal women. The impact of adjuvant therapy on quality of life is addressed, as is the role of doxorubicin in adjuvant chemotherapy. The value of high dose adjuvant chemotherapy and late effects of adjuvant therapy are also examined.

The Use of Hematopoietic Growth Factors to Support Cytotoxic Chemotherapy for Patients with Breast Cancer
George D. Demetri

The rationale for the uses of hematopoietic growth factors in the treatment of breast cancer is reviewed. The historical background of development of these novel therapeutic agents is also summarized as it pertains to patients undergoing myelosuppressive treatments. Important areas of controversy in the clinical uses of hematopoietic growth factors are identified, and future research directions in this field are discussed.

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PACLITAXEL (TAXOL) IN BREAST CANCER

Susan G. Arbuck, MD, Andrew Dorr, MD, and Michael A. Friedman, MD

Thirty years ago, samples of Taxus brevifolia, the Pacific yew tree, were collected from the old growth forests of the Pacific northwest, as part of a National Cancer Institute (NCI) program to screen natural products for anticancer activity. Preliminary screening indicated that an extract from the tree had activity against several murine and human tumor cell lines, including the human MX-1 breast cancer xenograft model. Paclitaxel, the active component of the extract, was isolated in pure form in 1969, and its structure was described by Wani, Taylor, and Wall in 1971 (Fig. 1). Paclitaxel is a complex diterpene with a taxane ring system composed of a four-membered oxetane ring and an ester side chain at position C-13 (necessary for cytotoxic activity in mammalian cells).

Paclitaxel has a novel mechanism of action. Although relatively little is known about mechanisms of clinical resistance in human tumors, a great deal is known about clinical toxicity and clinical activity. This article summarizes selected background information and the results of the clinical breast cancer trials. Many questions regarding how to optimally incorporate this new active agent into treatment for breast cancer patients remain unresolved; studies addressing these questions will be described.

MECHANISM OF ACTION

Schiff and Horwitz described paclitaxel's unique mechanism of cytotoxicity in 1979. In contrast to other antimitotic agents, such as vinca alkaloids and colchicine, which inhibit the polymerization of tubulin, paclitaxel promotes the assembly of tubulin and stabilizes the resulting microtubules.

Microtubules are important structural elements in eukaryotic cells. In addition to forming the mitotic spindle and channels for neurotransmitter secretion,
they regulate cell shape, anchor surface receptors in the plasma membrane, and affect motility of cilia. In the presence of paclitaxel, tubulin polymerization is promoted. Thus, the normal equilibrium of assembly and disassembly is shifted toward microtubule formation. Disruption of this equilibrium interferes with cell division and normal cellular activities involving microtubules.

Paclitaxel is a potent inhibitor of eukaryotic cell replication, and it blocks cells in late G2-mitotic phase of the cell cycle. Mitotic arrest has been observed in normal esophagus, stomach, small intestine, colon, liver, skin, bone marrow, and testis specimens obtained at autopsy from a patient who received paclitaxel 11 days before death.

PHARMACOLOGY

Paclitaxel disposition is characterized by a biexponential process, with a beta half-life of 4 to 6 hours. Pharmacokinetic parameters for 3, 6, 24, and 96 hour
administration schedules are summarized in Table 1. Peak plasma concentrations achieved with all schedules are within the range of drug concentrations reported to induce biologic and cytotoxic effects in vitro (0.01 to greater than 1 µM).\textsuperscript{1,36} Paclitaxel is extensively bound to plasma proteins (95% to 98%).\textsuperscript{22,26,63} Nevertheless, the drug is readily eliminated from plasma.\textsuperscript{26,62,63}

Renal clearance has accounted for an insignificant proportion of total systemic clearance (approximately 5%). The principal mechanisms of systemic clearance have not been defined precisely, suggesting that metabolism, biliary excretion, or extensive tissue binding are responsible for the bulk of systemic clearance. High paclitaxel concentrations and hydroxylated metabolites have been found in both rat and human bile.\textsuperscript{26,67}

Recently, two groups reported that clearance decreased with increasing dose, indicating that paclitaxel elimination was nonlinear.\textsuperscript{23,50} With nonlinear elimination, a small increase in dose or decrease in infusion duration can result in a large increase in total drug exposure and toxicity.

With evidence of increasingly broad clinical activity, a phase I trial was initiated to evaluate the toxicity and pharmacokinetics of paclitaxel in patients with abnormal liver function. This study will determine whether paclitaxel can be used safely in patients with hepatic impairment and, if so, determine necessary dose adjustments.

**TOXICITY**

**Leukopenia**

Phase I studies of paclitaxel demonstrated that leukopenia was frequent and dose-limiting on all schedules evaluated, whereas thrombocytopenia was rare. When administered over 24 hours, doses of 135 to 250 mg/m² caused grade III and IV neutropenia in the majority of patients, usually 8 to 11 days after drug administration. Recovery usually occurred by day 15 to 21, permitting re-treatment every 3 weeks.\textsuperscript{35} Recent data indicate that in addition to being dose-dependent, neutropenia is schedule-dependent, with less neutropenia occurring on the 3-hour schedule compared with the 24-hour schedule.\textsuperscript{51} Neutropenia does not worsen with repetitive dosing.

**Hypersensitivity Reactions**

Because of its limited aqueous solubility, paclitaxel is formulated in Cremophor EL and ethanol. Cremophor EL has been associated with bronchospasm, hypotension, and other manifestations of hypersensitivity, particularly following

<table>
<thead>
<tr>
<th>Schedule (hr)</th>
<th>T½β (hr)</th>
<th>CI (mL/min/m²)</th>
<th>VDss (L/m²)</th>
<th>Cmax* (µM)</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
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<td>6.4</td>
<td>195</td>
<td>59</td>
<td>3–4</td>
<td>26, 63</td>
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<td>3.9</td>
<td>993</td>
<td>55</td>
<td>0.7–0.9</td>
<td>62</td>
</tr>
<tr>
<td>96</td>
<td></td>
<td>478</td>
<td></td>
<td>0.05–0.07</td>
<td>64</td>
</tr>
</tbody>
</table>

\*At doses recommended for phase II evaluation

\(T_{1/2}\beta\) = beta half-life; CI = clearance; VDss = volume of distribution; Cmax = peak plasma concentration
rapid administration. Although Cremophor EL is used to formulate other drugs, the paclitaxel formulation requires the highest Cremophor EL concentration per dose.

Hypersensitivity reactions were reported in as many as 18% of patients in early phase I trials. Allergic manifestations varied in severity and included anaphylaxis, dyspnea, hypotension, flushing, urticaria, rash, and pruritus. Therefore, a routine premedication regimen was adopted: oral or intravenous dexamethasone, 20 mg (6 and 12 hours pre-treatment); diphenhydramine, 50 mg; and an H1 blocker (usually cimetidine, 300 mg) intravenously 30 minutes before paclitaxel. With routine premedication paclitaxel can be administered safely over 3 as well as 24 hours. In one trial, severe hypersensitivity reactions occurred in 2.2% of patients treated on the 3-hour schedule and in 1.2% of those on the 24-hour schedule.

Although Cremophor EL may be responsible for the hypersensitivity phenomena, some contribution of paclitaxel itself is possible. Anaphylaxis and angioedema have been reported in a teenager who chewed yew needles. Hypersensitivity reactions also occur in patients who receive docetaxel (Taxotere), a semisynthetic analogue of paclitaxel that is partially synthesized from 10-deacetylbaccatin III, isolated from the needles of the European yew, Taxus baccata. Docetaxel is formulated with polysorbate (Tween-80), which also has been associated with hypersensitivity and skin reactions. At present, it is not possible to determine the relative contribution of the taxanes versus the formulations to the hypersensitivity reactions.

**Neurotoxicity**

Because neutropenia was dose-limiting in phase I trials, granulocyte colony-stimulating factor (G-CSF) was added in an effort to administer higher doses of paclitaxel. At doses of 250 mg/m² or higher every 3 weeks, peripheral neuropathy, characterized primarily by sensory symptoms such as paresthesias and numbness in a stocking-glove distribution, become dose-limiting. Symptoms often begin 24 to 72 hours after treatment. Although neurotoxicity is usually reversible, it is also cumulative. In some cases recovery requires many months. Patients who develop grade 3 or worse neuropathy (severe objective sensory loss, paresthesias, or weakness with functional impairment) can generally be retreated at a lower dose once they recover to grade 1 or less neurotoxicity (mild paresthesias, or loss of deep tendon reflexes or subjective weakness with no objective findings).

Transient myalgias are frequent occurrences following moderate to high doses of paclitaxel. Typically, patients develop discomfort 2 to 3 days following treatment, with resolution in 5 or 6 days. Some investigators have noted more troublesome myalgia in association with G-CSF administration.

Motor neuropathy has also been reported, generally as a consequence of higher paclitaxel doses, and in patients with other risk factors for neuropathy. Possible autonomic neuropathy manifested as hypotension has been reported rarely.

**Cardiac Toxicity**

Concerns about anaphylaxis early in clinical development led investigators at Johns Hopkins Cancer Center to perform continuous cardiac monitoring dur-
ing paclitaxel administration. Sinus bradycardia was documented in 29% of 40 patients but was rarely clinically significant.29 Other cardiac changes were documented in 5% of 144 monitored patients. These events included heart block, nonsustained ventricular tachycardia, other ventricular and atrial arrhythmias, myocardial ischemia, and infarction. A causal relationship between paclitaxel and most ischemia and tachyarrhythmia episodes is uncertain.30 37 Most arrhythmias were asymptomatic.

Once cardiac events were reported, patients with potential cardiac risk factors were excluded from paclitaxel trials to maximize the safety of patients receiving this investigational drug. Patients expected to be intolerant of bradycardia, including those with a history of congestive heart failure or angina, and those who had sustained a myocardial infarction within 6 months, were deemed ineligible. Patients with arrhythmias and those on medications known to alter cardiac conduction, including digoxin, calcium channel blockers, and beta-adrenergic blockers, were also frequently excluded. The actual risk associated with these clinical circumstances remains unknown.

Toxicology reports from human yew poisonings and structural similarities of paclitaxel with taxine B, a known cardiac toxin, support the conclusion that paclitaxel has cardiac effects.3 Nevertheless, most of the arrhythmias are asymptomatic, and the incidence of cardiac events is very low in studies performed without routine continuous cardiac monitoring. Based on experience to date, patients without obvious risk factors do not require continuous cardiac monitoring. Current data are insufficient to make recommendations for patients with significant cardiac risk factors, because they have been excluded from most paclitaxel trials. In the absence of such information, a treating physician should consider potential risks and potential benefit for each patient. Careful vigilance by treating physicians and continued reporting of adverse cardiac events to the National Cancer Institute (NCI) for NCI-sponsored trials, and to the Food and Drug Administration (FDA) when patients have been treated with commercial drug, should generate additional information to help determine whether such patients are at increased risk of adverse cardiac events or if the concern is unwarranted.

Other Toxicities

Complete or nearly complete alopecia occurs in all patients treated with paclitaxel. Fatigue and arthralgia, in conjunction with myalgia, are common at the higher doses. Mucositis is also frequent at high doses and appears to be more common on the 96-hour continuous infusion schedule.6 5 Nausea, vomiting, and diarrhea occur but are rarely severe. Taste and mood alterations, hepatic enzyme abnormalities, and seizures have been reported rarely.

If infiltration occurs during administration, taxol may cause local erythema, tenderness, and induration. Rare reports of local ulceration or cellulitis following infiltration have been received. These complications healed with conservative management. Cremophor is a known vesicant and may contribute to local reactions.

PHASE II CLINICAL TRIALS IN BREAST CANCER PATIENTS

In 1986, the first phase II breast cancer trial was initiated at the MD Anderson Cancer Center. Twenty-five patients who had received no more than one
prior chemotherapy regimen (as adjuvant therapy or for metastatic disease) were treated with paclitaxel by 24-hour infusion every 3 weeks (Table 2). Eighteen patients were treated with 250 mg/m², and seven received 200 mg/m² (due to predicted poor hematologic tolerance). Fourteen patients had received prior adjuvant therapy, and 11 had received one combination chemotherapy regimen for metastatic disease. The objective response rate was 56% (including 12% complete responses). The investigators noted that in only two patients (8%) did paclitaxel fail to cause any regression or stabilization of tumor.

The median time to best response was 3.5 months (range, 1 to 7 months), and the median duration of response was greater than 10 months. The median time to disease progression was 9 months (range, 5 to 13+ months), and the median survival was 24 months (range, 5 to 34+ months).

Dose reductions were required for a neutrophil nadir of less than 250/µL or for infection associated with granulocytopenia. Most patients had grade 4 neutropenia; the median duration was 7 days. Thirty-six percent of patients had febrile neutropenia. The median administered dose was 200 mg/m². In future studies the investigators recommended dose reductions for febrile neutropenia and not for neutropenia in the absence of clinical consequences. They also suggested evaluation of hematologic growth factors to determine whether the severity and duration of granulocytopenia could be reduced.

These impressive results stimulated a second phase II trial in breast cancer at Memorial Sloan-Kettering Cancer Center (MSKCC). In this study, eligibility was restricted to patients who had no prior chemotherapy for metastatic breast cancer. This study differed in that all patients began treatment with paclitaxel, 250 mg/m², and all patients received G-CSF routinely with each cycle. However, dose reductions were still mandated for a neutrophil nadir less than 250/µL.

Twenty-eight patients were entered. Sixty-one percent had received prior adjuvant chemotherapy, with a median time interval from completion of adjuvant therapy to study entry of 20 months (range, 12 to 47 months). Eighty-two percent had two or more sites of metastatic disease; 39% had at least three sites. The results of this trial were similar to those of the MD Anderson study (see Table 2). Sixty-two percent of 26 evaluable patients responded (including 8% with complete responses). Responses were observed in all sites of metastatic disease, including previously irradiated chest wall disease in one patient. Another patient experienced reossification of bony metastases with associated pain relief. The median time to first objective response was 6 weeks (range, 1 to 14 weeks). Because the protocol called for drug discontinuation two cycles beyond best response, the response duration on this trial could not be determined; most patients proceeded directly to alternative therapies, including high-dose chemotherapy with autologous bone marrow support.

Despite the routine administration of G-CSF in this study, dose reductions were necessary for the second cycle in 12 of 26 patients, primarily for granulocyte nadir counts less than 250/µL. Febrile neutropenia occurred in 6 of 28 patients (21%). G-CSF did not ameliorate the neutrophil nadir, which occurred approximately 1 week after paclitaxel; however, the median time to recovery to more than 500 neutrophils/µL was 3.5 days (range, 1 to 8 days), compared with 7 days in the previous study without G-CSF.

These two phase II trials demonstrated paclitaxel's antitumor activity in a defined subset of patients with metastatic breast cancer. Both studies were performed in patients with good performance status and organ function, and with minimal or no prior treatment for advanced disease. Although these single-agent response rates are among the best that have been reported, combination therapies also produce similar or superior complete and overall response rates. Further-
Table 2. PACLITAXEL RESPONSE RATES IN METASTATIC BREAST CANCER

<table>
<thead>
<tr>
<th>Institution (Ref.)</th>
<th>Dose (mg/m²)*</th>
<th>Prior Chemotherapy† (Prior Anthracycline)</th>
<th>No. Entered</th>
<th>No. Evaluable</th>
<th>No. Responses</th>
<th>% CR + PR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD Anderson†</td>
<td>250 (200)§</td>
<td>≤1 (6 resistant)</td>
<td>25</td>
<td>25</td>
<td>3</td>
<td>56 (35–76)</td>
</tr>
<tr>
<td>MSKCC†</td>
<td>250 + G-CSF</td>
<td>0 (NA)</td>
<td>28</td>
<td>26</td>
<td>3</td>
<td>62 (41–80)</td>
</tr>
<tr>
<td>MSKCC†</td>
<td>200 + G-CSF</td>
<td>≥2 (all)</td>
<td>51</td>
<td>51</td>
<td>0</td>
<td>26 (14–40)</td>
</tr>
<tr>
<td>MD Anderson‡</td>
<td>150 (135)§</td>
<td>≥3 (all)</td>
<td>NA</td>
<td>18</td>
<td>0</td>
<td>33 (13–59)</td>
</tr>
<tr>
<td>MD Anderson‡</td>
<td>150 (135)§</td>
<td>≥2 (all)</td>
<td>NA</td>
<td>5</td>
<td>5</td>
<td>33 (13–59)</td>
</tr>
<tr>
<td>NCI Treatment Referral Center‡</td>
<td>175</td>
<td>≥1 (all)</td>
<td>267</td>
<td>NA</td>
<td>0</td>
<td>53 (28–77)</td>
</tr>
<tr>
<td>NCI Medicine Branch‡</td>
<td>140 + G-CSF [96 hr]</td>
<td>≥1 (all)</td>
<td>22</td>
<td>17</td>
<td>0</td>
<td>53 (28–77)</td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>135 [3 hr]</td>
<td>≤1 (77%)</td>
<td>417</td>
<td>117</td>
<td>3</td>
<td>26 (18–35)</td>
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<td>Study Group‡</td>
<td>175 [3 hr]</td>
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</tr>
</tbody>
</table>

*Pacitaxel was administered by 24-hour infusion unless otherwise stated
†Prior therapy refers to the number of prior chemotherapy regimens for metastatic disease
‡Preliminary report
§Patients with predicted poor hematologic tolerance received lower starting dose
NA = not available; G-CSF = granulocyte colony-stimulating factor; CR = complete response; PR = partial response; CI = confidence interval
more, few other drugs have been evaluated as single agents in patients with so little prior chemotherapy. These promising results led to additional studies to evaluate paclitaxel's antitumor activity in other patient populations, and to explore combination therapies that might produce higher response rates (especially complete responses).

**Paclitaxel in Patients with Refractory Metastatic Breast Cancer**

Table 2 also summarizes preliminary results of phase II trials in more heavily pretreated patients. In the second MSKCC study, patients who had received at least two prior regimens for metastatic disease (including doxorubicin or mitozantrone) were treated with paclitaxel, 200 mg/m² every 21 days. G-CSF was administered on days 3 to 10. The median age of patients entered on this trial was 47 years, with a median Karnofsky performance status of 70 (range, 60 to 90). In an interim report of the data as of November 1992, 13 of 51 patients (25%) had partial responses, with a median response duration of 16+ weeks (range, 4 to 28+ weeks). The investigators noted that responses were continuing to evolve in 16 patients. The median number of disease sites in this study was three (range, one to seven sites). Forty-four of 51 patients had multiple sites of metastasis. The distribution of sites of metastasis was bone, 47%; lymph nodes, 43%; liver, 33%; skin and soft tissue, 47%; and lung or pleura, 45%. Responses were seen in all sites of measurable disease.

In this second MSKCC trial and in subsequent trials at that institution, the paclitaxel dose was decreased for episodes of febrile neutropenia, but not for a predetermined degree or duration of neutropenia. Nevertheless, 47% of 51 patients required a dose reduction. In this more heavily pretreated population, nine patients had febrile neutropenia, four had grade 3 or 4 mucositis, four had grade 3 myalgia/arthritis, and three had grade 3 peripheral neuropathy. Ten of 51 patients who required dose reductions had platelet counts less than 50,000/µL. This result contrasts with this group's previous study: only 1 of 26 patients with minimal prior treatment developed significant thrombocytopenia. Although the starting dose was 200 mg/m² and G-CSF was used, the median delivered dose was 150 mg/m².

An interim report of the MD Anderson study of paclitaxel in patients with refractory breast cancer is also available. Patients who had received three or more chemotherapy regimens for metastatic breast cancer (including doxorubicin) received paclitaxel, 150 mg/m² (or 135 mg/m² if they had also received extensive prior radiation therapy). Hematopoietic colony stimulating factors were not administered. At the time of the preliminary report, 6 of 18 evaluable patients had experienced partial responses. In another preliminary report of the first 39 courses in 12 of these patients, 33% of patients had febrile neutropenia, and 17% had documented infection. Neutropenic fever complicated 21% of 39 courses. Thus, paclitaxel has activity in heavily pretreated patients. Although the delivered dose intensity was lower, the incidence of neutropenic fever was similar to that reported in patients with less prior chemotherapy. Thrombocytopenia was more common in heavily pretreated patients who received a paclitaxel dose of 200 mg/m².

Other schedules of paclitaxel administration have been studied and are included in Table 2. It is not clear which schedule(s) might be optimal. A 96-hour infusion regimen developed at the NCI Medicine Branch has been administered...
to 22 doxorubicin-resistant patients who were previously treated with one or more prior chemotherapy regimens. A preliminary communication reported partial responses in 9 of 17 evaluable patients.44

A preliminary pooled response rate is available for 117 of 417 breast cancer patients randomized to receive paclitaxel by 3-hour infusion at doses of 135 or 175 mg/m².29 These preliminary data from a phase III trial are included in Table 2 because they are the first available for the 3-hour infusion in breast cancer and because responses have not yet been reported by dose. These patients had received no more than one prior chemotherapy regimen for metastatic breast cancer. Seventy-seven percent had prior exposure to an anthracycline or anthra- cenedione. The pooled response rate was 27%.

**Treatment Referral Center Protocol**

The NCI Treatment Referral Center was established to provide access to active investigational drugs for patients with disease refractory to conventional therapy. Based on the reports of paclitaxel's activity in refractory breast cancer patients, Treatment Referral Center protocol 92-02 for women with breast cancer who had received two or more prior regimens for metastatic disease and who were refractory to, or not candidates for, doxorubicin, enrolled 257 women between November 1992 and February 1993. Although only preliminary results are available, they are consistent with those reported in heavily pretreated patients (data on file, CTEP, NCI).

**Doxorubicin-Resistant Breast Cancer**

Preclinical in vitro studies demonstrated marginal cross-resistance between paclitaxel and doxorubicin.59 However, Holmes and colleagues18 noted that in their initial phase II trial in women with no more than one prior chemotherapy regimen, six patients were doxorubicin-resistant; one relapsed at completion of adjuvant therapy, and five relapsed after an initial response. Three of these six patients responded to paclitaxel.

The Memorial investigators recently summarized their experience with 72 patients who had received at least one prior cytotoxic regimen for metastatic breast cancer (median, 2; range, 1 to 6).45 This report also includes the 51 previously described patients who had received two or more prior chemotherapy regimens for metastatic disease. Patients who had received one prior regimen received paclitaxel, 250 mg/m², and those who had received more than one prior regimen received 200 mg/m² by 24-hour infusion. All patients received G-CSF. Thirty-seven patients had doxorubicin-refractory disease, 31 had responded to doxorubicin with subsequent progression of disease, and two others had stable disease while on doxorubicin. Only two patients had not received prior doxorubicin. Overall, 20 of 72 patients responded to paclitaxel (28%; 95% confidence interval [CI], 18 to 40). Eight of 21 patients who had received one prior chemotherapy regimen responded (38%; 95% CI, 18 to 62); 7 of 22 who had received two prior regimens responded (32%; 95% CI, 14 to 55) and 5 of 29 who had received three or more prior chemotherapy regimens responded (17%; 95% CI, 6 to 36). Responses were continuing to evolve in 24 patients still undergoing therapy at the time of the report. Thus, although the response rate appears lower for patients who have received multiple prior chemotherapy regimens, resistance
ARBUCK et al

to doxorubicin does not consistently predict resistance to paclitaxel. Although doxorubicin is a drug that induces the P170-glycoprotein phenotype associated with multidrug resistance, other resistance mechanisms have been documented, including altered topoisomerase-I activity. 9

MECHANISMS OF RESISTANCE

Paclitaxel is a hydrophobic, natural molecule. These characteristics are often associated with induction of the multidrug resistance (mdr) phenotype. Multidrug resistant CHO and P388 cells are 36- and 283-fold more resistant to paclitaxel than are the parental cell lines. 9 However, it is not yet known whether the multidrug resistance phenotype plays an important clinical role in drug resistance in patients with breast cancer, or in patients with other human tumors.

Several clinical trials in breast cancer will attempt to assess the importance of the mdr phenotype in resistance to paclitaxel. These studies incorporate pre-treatment biopsies for mdr determination. In others, patients are randomized to paclitaxel or an mdr-associated drug (doxorubicin in one study, vinblastine in another) with cross-over to the alternate drug at progression. Because the trial with vinblastine, TRC 93-01, includes two drugs with opposing biologic effects (polymerization or depolymerization) on the same target (tubulin), it will be interesting to determine whether collateral sensitivity can be demonstrated.

Because some agents can ameliorate paclitaxel resistance that is mediated by mdr in vitro, 21, 28 phase I trials of paclitaxel in combination with R-verapamil, quinine, and cyclosporin are underway. However, if mdr is not a common mechanism of clinical resistance in breast cancer patients, this approach would not be expected to play a major therapeutic role. Interestingly, the Cremophor EL in which paclitaxel is formulated has been shown to overcome mdr in some systems. 66

When other classical antimitotic drugs are used to select resistant Chinese hamster ovary (CHO) cells in the laboratory, mutant cells usually demonstrate the mdr phenotype. However, with paclitaxel, mutant cells with tubulin alterations that decrease microtubule assembly have been selected. 5 Paclitaxel-resistant CHO cells have been developed with altered α- or β-tubulin, 90 or with a normal cytoplasmic microtubule complex but impaired ability to form a mitotic spindle in the absence of paclitaxel. 7 Cells with altered tubulins underlying paclitaxel resistance may exhibit increased sensitivity (so-called collateral sensitivity) to drugs such as vinblastine that act to destabilize microtubules. 58

It is important that techniques to evaluate other potential mechanisms of resistance, particularly tubulin abnormalities, be refined so that these can be evaluated clinically. Antibodies to tubulin are available and preliminary studies are underway in selected tumor types where tissue is accessible, including locally advanced breast cancer. Based on their phase I study in leukemia, Rowinsky et al. 36 suggested that in vitro microtubule bundling in tumor cells might prove useful to predict responsiveness in human tumors. Studies attempting to assess microtubule bundling in tumor cells are difficult, particularly in solid tumors, but several are ongoing.

COMBINATION THERAPY WITH PACLITAXEL

The best therapeutic results in cancer chemotherapy are usually achieved with combinations of two or more drugs. When possible, efforts are made to combine full doses of non-cross resistant drugs with single-agent activity, differ-
ing mechanisms of action, and nonoverlapping toxicity. Because paclitaxel is most frequently associated with partial but not complete responses, identification of effective drug combinations is an important goal. With its unique mechanism of action, paclitaxel provides both opportunities and challenges for development of combination chemotherapy.

There are few preclinical examples in which paclitaxel in combination with another drug was better than either drug alone.\(^2\)\(^3\)\(^4\) Furthermore, the sequence of administration appears to be an important determinant of the efficacy and toxicity of paclitaxel combination chemotherapy. For example, in murine 16/C and human MCF7 mammary adenocarcinoma xenograft models, superadditive activity was demonstrated with doxorubicin pretreatment, and subadditive activity with concomitant administration or paclitaxel pretreatment.\(^6\)\(^0\) In two clinical studies, more toxicity was observed when paclitaxel was administered prior to doxorubicin.\(^3\)\(^5\)\(^6\)

Unfortunately, these preclinical data were not available when clinical studies were initiated. Thus, clinical studies have empirically explored several schedules, dosages, and sequences. One pilot trial and three phase I studies of different schedules of paclitaxel and doxorubicin have been conducted (Table 3).\(^1\)\(^0\), \(^1\)\(^3\), \(^4\)\(^9\)

The toxicities of the combination are primarily mucositis and neutropenia. Typhilitis (inflammation of the cecum) was dose-limiting on the NCI Medicine Branch study. As noted, toxicities appear to depend upon the sequence and infusion schedules of the two drugs.

Although these were phase I trials and response rates were not the primary endpoint, those reported are included in Table 3. The response rates are high, but this combination of two very active drugs in breast cancer would be of particular interest if it increased the complete response rate. Although some trials included patients with prior doxorubicin, patients on these trials had not received much prior chemotherapy. At present, it is not clear how best to combine these two agents; their utility in combination in this disease also is not clear.

Other paclitaxel combinations are being studied to develop treatment regimens suitable for phase III evaluation in breast cancer. Ongoing phase I trials include paclitaxel in combination with carboplatin, cyclophosphamide, edatrexate, etoposide, 5-fluorouracil ± leucovorin, ifosfamide, methotrexate, estramustine, and topotecan. Because of documented synergy of paclitaxel and cisplatin, and the activity of both drugs in breast cancer, phase II studies of this combination are accruing patients.

The challenge of combining paclitaxel with other drugs is even more complex when the second drug also targets microtubules. The combination of a drug that stabilizes microtubules with one that destabilizes them may be antagonistic with less anticancer activity, or substantially more cytotoxic, with adverse effects also manifested in normal host cells. In addition, tumor cells that develop resistance to a drug that destabilizes microtubules might develop collateral sensitivity to paclitaxel, which stabilizes and polymerizes them.\(^5\)\(^8\)

### PACLITAXEL AS A RADIATION SENSITIZER

Paclitaxel concentrations as low as 10 to 100 nM enhanced the effects of ionizing radiation in the relatively radioresistant G18 astrocytoma cell line.\(^5\)\(^4\) The degree of enhanced cell killing depended upon paclitaxel concentration and the fraction of cells in G\(_2\) or M phases of the cell cycle. Because paclitaxel blocks cells in G\(_2\)/M, and cells in G\(_2\)/M are more sensitive to radiation, radiation sensitization has been attributed to the kinetic perturbation induced by paclitaxel.\(^5\)\(^4\) How-
<table>
<thead>
<tr>
<th>Institution (Ref.)</th>
<th>Schedule</th>
<th>MTD (Total mg/m²)</th>
<th>G-CSF</th>
<th>DLT</th>
<th>Prior Therapy</th>
<th>Prior Doxorubicin</th>
<th>No. Patients</th>
<th>% Response*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI Medicine Branch</td>
<td>Concurrent 72-hr infusion</td>
<td>Pac 160 + Dox 75</td>
<td>Yes</td>
<td>Neutropenia, diarrhea, fever, thrombocytopenia</td>
<td>Adjuvant</td>
<td>No</td>
<td>18</td>
<td>6, 56, 22, 17, 5</td>
<td>Median duration of response, 8+ months</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>Pac 24 hr, then Dox 48 hr</td>
<td>Pac 125 Dox 48</td>
<td>Yes</td>
<td>Neutropenia, fever, stomatitis, thrombocytopenia</td>
<td>Adjuvant</td>
<td>Yes</td>
<td>10</td>
<td>10, 70, 10, 10, 0</td>
<td>Results suggest sequence-dependent toxicity</td>
</tr>
<tr>
<td>Indiana</td>
<td>Dox 48 hr, then Pac 24 hr</td>
<td>Dox 60 Pac 150 Dox 50 Pac 150</td>
<td>Yes</td>
<td>Neutropenia, mucositis</td>
<td>≤ 1 for metastatic disease</td>
<td>Yes</td>
<td>21</td>
<td>6, 44, 44, 6, 0</td>
<td>3 patients had Grade 3 or 4 mucositis at these doses when Taxol was given first. Suggests sequence-dependent toxicity</td>
</tr>
<tr>
<td>Indiana (pilot)**</td>
<td>Day 1: Pac 24 hr, Day 22: Dox IV push</td>
<td>Pac 200 Dox 75</td>
<td>No</td>
<td>Neutropenia, fever</td>
<td>≤ 1 for metastatic disease</td>
<td>No</td>
<td>12</td>
<td>17, 42, NA, 17, 25</td>
<td>Suboptimal dose intensity</td>
</tr>
<tr>
<td>Hopkins</td>
<td>Pac 3 hr; Dox IV push, and reverse sequence</td>
<td>Too early</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Response information is summarized although response is not the major endpoint of phase I trials where the majority of patients receive doses less than those recommended for phase II evaluation. 

Prog = progression; Pac = paclitaxel; Dox = doxorubicin; NA = not available; MTD = maximally tolerated dose; G-CSF = granulocyte colony-stimulating factor; DLT = dose-limiting toxicity; CR = complete response; PR = partial response; MR = minor response; SD = stable disease.
ever, in the MCF-7 human breast carcinoma cell line, paclitaxel concentrations of 1 to 10 nM, which were sufficient to induce G2/M block, did not increase the effectiveness of radiation, whereas higher paclitaxel concentrations did increase the effectiveness of radiation. In contrast, A549 human lung adenocarcinoma cells were not sensitized to radiation by paclitaxel at any concentration tested. Thus, the mechanism for radiation sensitization remains incompletely understood.

The combination of radiotherapy and paclitaxel has potential application in several tumor types, including breast cancer. Phase I studies of the combination, with paclitaxel administered on a variety of schedules, are underway.

**PHASE III TRIALS**

**Optimal Dose and Schedule**

Currently the optimal dose and schedule for paclitaxel administration are unknown. The 24-hour schedule was adopted for initial phase II evaluation because it was associated with a lower incidence of severe hypersensitivity reactions. However, with premedications, paclitaxel can be administered safely over 3 hours. In preclinical studies, many investigators have reported that biologic and cytotoxic effects of paclitaxel increase as drug exposure is prolonged. Yet it is not clear that the 24-hour schedule represents prolonged exposure, or that it is better than the 3-hour schedule in patients.

In previously treated ovarian cancer, an important phase III randomized trial with a factorial design evaluated the 3- and 24-hour schedules, each with two paclitaxel doses, 135 and 175 mg/m². The 24-hour schedule was associated with more neutropenia than the 3-hour schedule, at both doses. Furthermore, the investigators reported that the 3-hour schedule was as effective as the 24-hour schedule. If the 3-hour schedule is as effective, it would be preferred because it is more convenient, less costly, and associated with less neutropenia. However, additional evaluation is required to confirm and extend these findings.

This trial did not evaluate paclitaxel at its maximally tolerated dose on either schedule, and recent data suggest (but do not prove) that there is a clinical benefit associated with higher doses. If a higher paclitaxel dose is more effective, it is essential to ask the schedule question at optimal doses, and G-CSF should be used if it is required to maintain dose intensity. Clearly, if dose intensity is not important, G-CSF, with its added expense and inconvenience, could be unnecessary.

In addition, because of the unexpected finding that the 24-hour schedule was more myelosuppressive, there has not been a proper evaluation of equitoxic doses. A phase I trial of paclitaxel on a 3-hour schedule determined that the maximally tolerated dose was 210 mg/m² without G-CSF and 250 mg/m² with G-CSF. A phase II study in breast cancer patients with less prior treatment is currently evaluating the feasibility and effectiveness of 250 mg/m² administered without G-CSF support.

Review of published data suggests that the addition of G-CSF does not result in a large difference in administered dose intensity or median nadir granulocyte count. The use of G-CSF does appear to shorten the duration of severe neutropenia from approximately 7 to 3.5 days. Because the risk of infection increases as the duration of neutropenia increases, one might expect that G-CSF treatment would be associated with a lower infection rate. However, the incidence of
infection appeared similar despite the use of G-CSF in one of two phase II breast cancer trials in minimally pretreated women with breast cancer.\textsuperscript{29,30} Randomized trials are required to determine whether G-CSF administration in conjunction with paclitaxel is associated with clinical benefit (increased response rate or decreased toxicity).

As already mentioned, Bristol-Myers Squibb sponsored a trial comparing 3-hour infusion of 175 or 135 mg/m\textsuperscript{2}.\textsuperscript{27} To further explore the dose-response relationship in breast cancer, two additional phase III studies are planned. In the Cancer and Leukemia Group B (CALGB) study, patients will receive paclitaxel over 3 hours at 175, 210, or 250 mg/m\textsuperscript{2} (Table 4). Although the dose difference between arms is not great, this study permits a determination of whether there is an advantage to administering a dose higher than 175 mg/m\textsuperscript{2}, which is well tolerated when given over 3 hours but probably not the highest dose that can be given. Furthermore, if a higher dose is useful, this study will determine whether G-CSF is required to obtain the best effect. Preclinical murine studies with M109 lung cancer demonstrated that there was a dose-response relationship up to a

<table>
<thead>
<tr>
<th>Table 4. PHASE III PACLITAXEL TRIALS IN ADVANCED BREAST CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCI-Sponsored Trials</strong></td>
</tr>
<tr>
<td>1. No prior chemotherapy for metastatic disease</td>
</tr>
<tr>
<td>ECOG</td>
</tr>
<tr>
<td>Paclitaxel 175 mg/m\textsuperscript{2} (24 hr)</td>
</tr>
<tr>
<td>vs Doxorubicin 60 mg/m\textsuperscript{2}</td>
</tr>
<tr>
<td>vs Paclitaxel 150 mg/m\textsuperscript{2} + doxorubicin 50 mg/m\textsuperscript{2} + G-CSF (Patients on single-agent arms cross-over at progression)</td>
</tr>
<tr>
<td>2. Symptomatic patients. Refractory to doxorubicin. No more than one prior chemotherapy regimen for metastatic disease</td>
</tr>
<tr>
<td>TRC 9301</td>
</tr>
<tr>
<td>Paclitaxel 210 mg/m\textsuperscript{2} (3 hr) every 3 weeks</td>
</tr>
<tr>
<td>vs Vinblastine 5.5 mg/m\textsuperscript{2} weekly</td>
</tr>
<tr>
<td>(Patients cross-over at progression)</td>
</tr>
<tr>
<td>3. One prior chemotherapy regimen for metastatic disease</td>
</tr>
<tr>
<td>Planned CALGB</td>
</tr>
<tr>
<td>Paclitaxel 175 mg/m\textsuperscript{2} (3 hr)</td>
</tr>
<tr>
<td>vs Paclitaxel 210 mg/m\textsuperscript{2} (3 hr)</td>
</tr>
<tr>
<td>vs Paclitaxel 250 mg/m\textsuperscript{2} (3 hr) + G-CSF</td>
</tr>
<tr>
<td>4. No prior chemotherapy for metastatic disease</td>
</tr>
<tr>
<td>Planned NSABP</td>
</tr>
<tr>
<td>Paclitaxel 250 mg/m\textsuperscript{2} (24 hr) + G-CSF</td>
</tr>
<tr>
<td>vs Paclitaxel 250 mg/m\textsuperscript{2} (3 hr) + G-CSF</td>
</tr>
<tr>
<td><strong>Bristol-Myers Squibb-Sponsored Trials</strong></td>
</tr>
<tr>
<td>5. ≤ 1 prior chemotherapy for metastatic disease</td>
</tr>
<tr>
<td>BMS 048 (accrual completed 6/92)</td>
</tr>
<tr>
<td>Paclitaxel 135 mg/m\textsuperscript{2} (3 hr)</td>
</tr>
<tr>
<td>vs Paclitaxel 175 mg/m\textsuperscript{2} (3 hr)</td>
</tr>
<tr>
<td>6. ≤ 1 prior chemotherapy for metastatic disease</td>
</tr>
<tr>
<td>BMS 071 (accrual completed 4/93)</td>
</tr>
<tr>
<td>Paclitaxel 175 mg/m\textsuperscript{2} (3 hr)</td>
</tr>
<tr>
<td>vs Paclitaxel 175 mg/m\textsuperscript{2} (24 hr)</td>
</tr>
<tr>
<td>Escalate dose if tolerated</td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group; TRC = Treatment Referral Center; CALGB = Cancer and Leukemia Group B; NSABP = National Surgical Adjuvant Breast and Bowel Project; G-CSF = granulocyte colony-stimulating factor
threshold dose, but no improvement when higher doses, including the maximum tolerated dose, were administered. If there is a similar threshold dose in cancer patients, it has not yet been demonstrated. This trial, and another in ovarian cancer that compares 135, 175, and 250 mg/m² (the latter with G-CSF), all administered over 24 hours, are attempting to address this issue in the clinic.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) will assess the schedule question by randomizing patients receiving first-line therapy for metastatic disease to paclitaxel, 250 mg/m², administered by 3- or 24-hour infusion. Patients will receive G-CSF on both arms. This study asks the schedule question at the maximal dose that can be administered on either schedule. The results will be useful when the next generation of adjuvant paclitaxel breast cancer trials is planned. In addition, accrual has been completed on a Bristol-Myers Squibb-sponsored trial that randomized patients with metastatic breast cancer to paclitaxel, 175 mg/m², over 3 or 24 hours. Dose escalations were permitted when tolerated.

Relative Efficacy of Paclitaxel

The Eastern Cooperative Oncology Group is conducting a phase III trial of doxorubicin versus paclitaxel versus the combination in women with metastatic breast cancer. Treatment Referral Center Protocol 93-01, which opened in July 1993, randomizes anthracycline-resistant patients to vinblastine or paclitaxel (see Table 4). Both of these studies incorporate quality of life evaluations.

Adjuvant Therapy of Breast Cancer

Single-agent paclitaxel is highly active in metastatic breast cancer and lacks cross-resistance with other commonly used breast cancer treatments including doxorubicin. The paclitaxel-doxorubicin combination has been most extensively studied in breast cancer. Although four phase I studies have been completed, no phase II trials have been performed. Whether any paclitaxel combination can be given without requirement for substantial dose reductions and whether the combination achieves a higher response rate over that which could be obtained with either single agent alone is unknown. Thus, no paclitaxel combination therapy is ready for adjuvant evaluation. The first paclitaxel adjuvant trials in breast cancer were designed to test whether adding this drug improves upon the results obtained with standard adjuvant therapy.

The NSABP will evaluate whether paclitaxel, 250 mg/m², administered over 3 hours in combination with G-CSF improves the results of their standard cyclophosphamide/doxorubicin program. The two regimens will be given sequentially. Prior to initiating the adjuvant trials two pilot trials are being performed in patients with metastatic breast cancer: one to ensure that full doses of the drugs can be administered safely in sequence, and the second to determine the response rate when paclitaxel, 250 mg/m², is administered by 3-hour infusion. It is anticipated that the adjuvant trial will start in 1994.

An intergroup trial in women with one to nine positive lymph nodes will randomize patients to standard or high-dose cyclophosphamide and doxorubicin. Following this therapy, patients will be randomized to paclitaxel, 175 mg/m², over 3 hours or no additional therapy.

TAXOTERE

Docetaxel (Taxotere) is a semisynthetic analogue of paclitaxel (see Fig. 1). It is synthesized from 10-deacetylbaclactin III, which is derived from the needles of
the European yew tree, Taxus baccata. Responses were observed in heavily pre-
treated breast cancer patients who participated in phase I trials of this agent.
Preliminary reports of phase II trials with this compound in breast cancer pa-
tients are summarized in Table 5. These results are also very encouraging.
Many of the toxicities observed with this agent are similar to those described
earlier for paclitaxel. These include neutropenia, peripheral neuropathy, and
alopecia. Although routine prophylactic medications to ameliorate severe hypersensi-
sitivity reactions were not utilized during phase I development of docetaxel,
regimens similar to those used with paclitaxel have been utilized during phase II
development. Peripheral edema or pleural effusions or both resulted in drug
discontinuation after a median of five cycles in 12 of 35 patients (12 of 24
responding patients) in one study. The etiology of these adverse effects is un-
clear. Patients are now receiving combinations of steroids, antihistamines, and
H2 antagonists for hypersensitivity prophylaxis, and it is hoped that these medici-
nations will prevent toxicity leading to discontinuation of effective therapy.

CONCLUSIONS

Paclitaxel is the prototype for a new class of anticancer drugs that has
focused attention on tubulin and microtubules as critical targets for chemother-
apy. Paclitaxel’s unique effects include its ability to polymerize tubulin into stable
microtubules in the absence of cofactors and to induce the formation of stable
microtubule bundles. However, the precise mechanism by which paclitaxel
causes cytotoxicity is poorly understood, as are its interactions with other factors
affecting microtubules. Mechanisms of de novo and acquired paclitaxel resistance
in human tumors are not well defined. As some of these questions become
resolved, our ability to exploit this important new drug in the clinic should
increase.

Paclitaxel and docetaxel are active drugs in breast cancer, even in heavily
pretreated patients with doxorubicin-refractory disease. The current clinical chal-
 lenges include integration of these new active drugs with their novel mechanisms
of action into effective combinations for therapy of breast cancer. Although identi-
fication of the optimal dose and most effective schedule appear to be less
important issues when therapy is administered with palliative intent, these are
critically important as we attempt to develop curative regimens for use in the
adjuvant setting. Phase III trials in breast cancer are designed to resolve some of
these questions.

Table 5. PRELIMINARY REPORTS OF DOCETAXEL (TAXOTERE) IN BREAST CANCER*

<table>
<thead>
<tr>
<th>Institution (Ref.)</th>
<th>No. Patients</th>
<th>No. with Prior Chemotherapy</th>
<th>No. Responses</th>
<th>% CR + PR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entered</td>
<td>Evaluable</td>
<td>Adjuvant</td>
<td>For Metastases</td>
</tr>
<tr>
<td>EORTC*</td>
<td>35</td>
<td>33</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>MSKCC*</td>
<td>18</td>
<td>14</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>NCIC</td>
<td>31</td>
<td>21</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>EORTC*</td>
<td>39</td>
<td>24</td>
<td>NA</td>
<td>24</td>
</tr>
</tbody>
</table>

*All patients received 100 mg/m2 over 1 hour without G-CSF (granulocyte colony-stimulating factor)
NA = not available; CR = complete response; PR = partial response; CI = confidence interval
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References


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