What Are the Roles of the Taxanes in Breast Cancer?

The taxanes are important new tools in our therapeutic armamentarium against breast cancer.

DR SLEDGE

Taxanes represent a new class of antineoplastic agents that act by shifting the dynamic equilibrium between tubulin and microtubules in the direction of microtubule assembly. The cells become blocked during the G₂ and M cell cycle phases and cannot form a normal mitotic spindle and divide. Essentially, these microtubules are excessively stable and therefore dysfunctional. Paclitaxel was the first of these drugs to be marketed in the United States. The drug demonstrates significant single-agent activity in a number of tumors, including breast cancer, in both previously untreated and previously treated disease (Table 1). Indeed, response rates to single-agent paclitaxel are similar to or better than those observed with standard combination regimens.

Recent investigations have focused on paclitaxel in combination with other active agents. The ECOG has combined paclitaxel with most other active agents for the treatment of metastatic breast cancer. At Indiana University, we evaluated paclitaxel in combination with the anthracyclines, cisplatin, and carboplatin. M.D. Anderson evaluated the efficacy of paclitaxel in combination with the vinca alkaloids, Johns Hopkins University combined paclitaxel with cyclophosphamide, and Vanderbilt University evaluated paclitaxel plus 5-FU.

We now have data from phase I and II trials suggesting safe paclitaxel-based combinations can be developed. In some settings, we have preliminary evidence that the combinations may be somewhat more active than single agents. Perhaps the most impressive data have come from the anthracycline/paclitaxel combinations evaluated by Gianni and colleagues at the National Tumor Institute in Milan, Italy. This group reported a 94% objective response rate and, perhaps more striking, a 40% complete remission rate for patients being treated for metastatic breast cancer (Table 2). Patients in this study received doxorubicin 60 mg/m² (IV bolus) and paclitaxel 200 mg/m² (three-hour infusion).

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of Evaluable Patients</th>
<th>Line</th>
<th>Dose (mg/m²)</th>
<th>Infusion Duration (hr)</th>
<th>OR (CR) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson²</td>
<td>14</td>
<td>First</td>
<td>250</td>
<td>24</td>
<td>57 (14)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Second</td>
<td>250</td>
<td>24</td>
<td>54 (6)</td>
</tr>
<tr>
<td>Lombardi²</td>
<td>19</td>
<td>First</td>
<td>135</td>
<td>24</td>
<td>32 (11)</td>
</tr>
<tr>
<td>MEKH²</td>
<td>26</td>
<td>First</td>
<td>250</td>
<td>24</td>
<td>60 (12)</td>
</tr>
<tr>
<td>MEKH²</td>
<td>51</td>
<td>Second</td>
<td>250</td>
<td>24</td>
<td>60 (12)</td>
</tr>
<tr>
<td>MEKH²</td>
<td>36</td>
<td>Second</td>
<td>250</td>
<td>24</td>
<td>60 (12)</td>
</tr>
<tr>
<td>NCI²</td>
<td>82</td>
<td>First</td>
<td>250</td>
<td>3</td>
<td>43 (17)</td>
</tr>
</tbody>
</table>

Table 1 -- Single-Agent Paclitaxel in Metastatic Breast Cancer

Table 2 -- Doxorubicin/Paclitaxel Results of Gianni et al. Combination Trial²}¹²
These early results prompted further evaluation of the paclitaxel/doxorubicin combination in phase II trials (Table 3). In addition, a number of phase III trials are evaluating a variety of issues regarding paclitaxel. I have led an Intergroup trial (ECOG, SWOG, and the North Central Cancer Treatment Group [NCCTG]) comparing single-agent doxorubicin, single-agent paclitaxel, and a combination of doxorubicin and paclitaxel. The results of this study will be presented at the American Society of Clinical Oncology (ASCO) annual meeting in 1997.

### Table 3 -- Paclitaxel Plus Doxorubicin: Phase II Studies in Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Previous Therapy</th>
<th>Number of Evaluable Patients</th>
<th>OR (%)/CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gianni et al 1995&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>P 200 mg/m&lt;sup&gt;2&lt;/sup&gt; IV, 3-h infusion + G-CSF Cycles repeated q 3 wk, maximum 8 cycles</td>
<td>No prior chemotherapy</td>
<td>32</td>
<td>94/41</td>
</tr>
<tr>
<td>Gianni et al 1996&lt;sup&gt;2&lt;/sup&gt;</td>
<td>P 200 mg/m&lt;sup&gt;2&lt;/sup&gt; IV, 3-h infusion + G-CSF Cycles repeated q 3 wk, 0 total dose = 480 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>No prior chemotherapy</td>
<td>47</td>
<td>94/40</td>
</tr>
<tr>
<td>Goi et al 1996&lt;sup&gt;3&lt;/sup&gt;</td>
<td>P 150-200 mg/m&lt;sup&gt;2&lt;/sup&gt; IV, 3-h infusion + G-CSF Cycles repeated q 3 wk, d 1 and 8</td>
<td>&lt; 1 prior adjuvant regimen; no prior anthracycline</td>
<td>29</td>
<td>83/24</td>
</tr>
<tr>
<td>Schwartz et al 1996&lt;sup&gt;2&lt;/sup&gt;</td>
<td>P 200 mg/m&lt;sup&gt;2&lt;/sup&gt; IV 2 to 3 h infusion + G-CSF Cycles repeated q 3 wk</td>
<td>No prior chemotherapy</td>
<td>28</td>
<td>80/28</td>
</tr>
<tr>
<td>Frassineti et al 1996&lt;sup&gt;2&lt;/sup&gt;</td>
<td>D 50 mg/m&lt;sup&gt;2&lt;/sup&gt; IV bolus 16 h before P P 130 to 250 mg/m&lt;sup&gt;2&lt;/sup&gt; IV, 3-h infusion Cycles repeated q 3 wk</td>
<td>No prior chemotherapy</td>
<td>32</td>
<td>76/01</td>
</tr>
<tr>
<td>Cavali et al 1996&lt;sup&gt;4&lt;/sup&gt;</td>
<td>P 200 mg/m&lt;sup&gt;2&lt;/sup&gt; IV 3-h infusion + G-CSF Cycles repeated q 3 wk</td>
<td>Prior chemotherapy allowed</td>
<td>27</td>
<td>48/4</td>
</tr>
</tbody>
</table>

OR = overall response
CR = complete response
P = paclitaxel
IV = intravenous
D = doxorubicin
G-CSF = granulocyte-colony-stimulating factor

Other trials are evaluating questions related to the dose intensity of paclitaxel. A current CALGB trial is comparing paclitaxel doses of 175 mg/m<sup>2</sup>, 210 mg/m<sup>2</sup>, and 250 mg/m<sup>2</sup>. The results of this trial should establish whether there is a reasonably steep dose response curve for paclitaxel above what we would consider the standard dose. Similarly, a prospective randomized trial by the NSABP is comparing paclitaxel infusion durations of three and 24 hours. We hope this trial will answer the important question of whether schedule differences are significant in the single-agent paclitaxel setting.

In the adjuvant setting, a current Intergroup trial is a double randomization for patients who are lymph-node-positive. This study includes an initial three-arm randomization evaluating different dose intensities of doxorubicin when given in combination with standard-dose cyclophosphamide. Patients are then randomized to paclitaxel 175 mg/m<sup>2</sup> (three-hour infusion) or no paclitaxel. This trial will complete accrual in late 1997.

Within the next few years, we should have good evidence to demonstrate whether paclitaxel adds significantly to the standard modalities in the micrometastatic setting. What has astonished me about this drug is how much we have done in a short time period. The experience of medical oncologists is that it frequently takes decades to adequately understand the mechanism of action and most appropriate uses of a new antineoplastic agent. However, paclitaxel has been available for only five or six years and we have multiple prospective randomized trials nearing completion that should greatly enhance our understanding of how well this drug works and in whom it should be used.

**DR ROWINSKY**

Whenever a clearly novel and unique new agent becomes available, it offers the possibility of changing our practice patterns. I am quite intrigued by the preliminary results of a randomized trial reported by the cooperative group in New Zealand and Australia. This study compared six months (eight cycles) of single-agent paclitaxel (200 mg/m<sup>2</sup> IV, three-hour infusion every three weeks) vs six months (six cycles) of CMFP (cyclophosphamide 100 mg/m<sup>2</sup>/day, orally days 1-14; methotrexate 40 mg/m<sup>2</sup>/IV days 1 and 8; 5-FU 600 mg/m<sup>2</sup>/IV days 1 and 8; and prednisolone 40 mg/m<sup>2</sup>/day, orally, days 1-14) in previously untreated metastatic breast cancer patients. Importantly, the CMFP regimen is approximately equitoxic to the paclitaxel dose used in the trial. The objective response in the first 100 evaluable patients was 31% (95% confidence interval = 19% to 45%) for patients receiving paclitaxel and 36% (95% confidence interval = 22% to 51%) for those receiving CMFP. Thus, these equitoxic regimens resulted in quite comparable response rates. Median time to progression was 5.5 months for paclitaxel and 6.4 months for CMFP; however, median survival was 16.5 months for patients receiving paclitaxel and 11.3 months for those receiving CMFP.

Although Bishop et al reported a similar incidence of grade 3/4 neutropenia for patients receiving either paclitaxel or CMFP, febrile neutropenia was the primary admission reason for two paclitaxel hospitalizations and 15 CMFP hospitalizations. No major infections occurred with paclitaxel treatment while 9% of patients receiving CMFP had major infections. In addition, mucositis developed in only 33% of patients receiving paclitaxel compared with 68% of patients receiving CMFP. Alopecia and peripheral neuropathy were more common in patients receiving paclitaxel setting.

These results suggest that single-agent paclitaxel, when used as a front-line outpatient therapy for metastatic breast cancer, provides disease control comparable to CMFP. More broadly, these results infer that a breakthrough new drug may truly modify our practice patterns with respect to the use of combination chemotherapy. Of course, these results need to be verified in other randomized clinical trials. I think the Intergroup trial described by Dr Sledge, which compares single-agent doxorubicin to single-agent paclitaxel to the combination of doxorubicin and paclitaxel, is intriguing; the results may help to verify these findings.

**DR HORTOBAGYI**

The other taxane currently available is docetaxel. This drug was developed later, and clinical trials lag by one to two years behind those of paclitaxel. While these two taxanes have many similarities, they are clearly two different drugs in terms of tubulin target, pharmacokinetics, schedule dependence, and clinical toxicity profile. There is also clear-cut demonstration that the two agents are not completely cross-resistant; responses have been observed with one after progression on the other.
Single-agent docetaxel trials in breast cancer have shown that the agent has similar encouraging activity to paclitaxel in terms of overall response rate (Table 4). In previously untreated patients, response rates to docetaxel 100 mg/m$^2$ range from 54% to 68%. In patients with previous exposure to standard chemotherapy or anthracycline-resistant disease, response rates range from 53% to 57%. Thus, docetaxel is clearly active in both previously treated and previously untreated patients. This is somewhat similar to paclitaxel, which also has shown activity in both settings (Table 2).

The single-agent data with docetaxel are similar to data obtained with standard combination chemotherapy regimens. Therefore, even in the absence of comparative trials, the data suggest that single-agent paclitaxel or docetaxel result in response rates and durations similar to what can be achieved with FAC, CMF, AC, or any of the commonly used regimens.

Docetaxel has a different toxicity profile from paclitaxel. While both agents share the ability to produce severe but rapidly reversible neutropenia, docetaxel also is associated with skin and nail changes and a cumulative toxicity of fluid retention, which can be prevented to some degree with three- to five-day concomitant dexamethasone administration. Alternatively, paclitaxel is more likely to produce peripheral neuropathy and acute muscle aches and pains but generally has not been associated with fluid retention.

Initial trials evaluating docetaxel combinations are just being completed. The drug has been combined with anthracyclines (epirubicin and doxorubicin); at this point, only early results are available. The docetaxel/doxorubicin combination has been reported to produce a 71% to 75% overall response rate and a 25% complete remission rate (Table 5). The maximum tolerated doses of doxorubicin and docetaxel are either 60 mg/m$^2$ and 75 mg/m$^2$, respectively, with growth factor support, or 60 mg/m$^2$ and 60 mg/m$^2$, respectively, without support.

Ongoing clinical trials are combining docetaxel with the vinca alkaloids, particularly vinorelbine. Docetaxel also has been combined with 5-FU, cisplatin, carboplatin, and a variety of other agents, similar to the paclitaxel developmental plan. In particular, three comparative trials with docetaxel are nearing completion or have completed accrual. One is a direct comparison of single-agent docetaxel with single-agent doxorubicin. In this trial, the docetaxel dose is 100 mg/m$^2$ and the doxorubicin dose is 75 mg/m$^2$. In a second trial, single-agent docetaxel is compared with mitomycin C and vinblastine, a commonly used regimen in the recent past for patients with anthracycline-refractory tumors. Finally, there are combination trials with doxorubicin, docetaxel, and cyclophosphamide in both the metastatic and adjuvant settings. These randomized trials recently opened and are accruing patients rapidly. There is also at least one new taxane in phase I trials and two or three others approaching initial phase I trials.

Docetaxel has not been studied in dose-intensive therapies since 100 mg/m$^2$ is probably equitoxic or equivalent to paclitaxel 250 mg/m$^2$. Comparatively, paclitaxel is a component of a number of high-dose chemotherapy regimens, administered either as a single high dose or as part of a multi-dose regimen using intermediate/high-dose or intermediate-dose chemotherapy.

This approach has been used at a number of centers including M.D. Anderson and Memorial Sloan-Kettering Cancer Center. The results of these trials are not readily available, although it is clear that doses higher than the standard dose are tolerable and tolerated if a limited number of cycles are administered.
Dose Response

DR HORTOBAGYI

In terms of dose response, it is important to mention that the two initial trials with paclitaxel were performed using a dose of 250 mg/m² administered as a 24-hour infusion. There is a third study of front-line single-agent paclitaxel 250 mg/m² administered as a three-hour infusion that also reported a 60% response rate. Every other follow-up study has used lower paclitaxel doses ranging from 175 to 210 mg/m². There were also trials in the anthracycline-resistant group that used paclitaxel 225 mg/m².

One randomized trial compared paclitaxel 135 to 175 mg/m² and showed a difference in response rate and time to progression. There is also the ongoing CALGB trial comparing paclitaxel 175, 210, and 250 mg/m² (three-hour infusion every three weeks) that Dr Sledge mentioned earlier, which I think is an extremely important trial.

DR VAUGHAN

My concern is that these trials are designed to answer the clinical question of which dose is the most reasonable to administer. Potentially, however, these trials may tell us only that the difference in benefit or toxicity between paclitaxel 225 and 250 mg/m² is not large enough to be statistically significant. These trials will not address the issues of infusion rate, schedule, or the role of supportive care.

DR HORTOBAGYI

I think there is a dose-response correlation with paclitaxel that remains insufficiently documented or studied. My initial recommendation was to compare paclitaxel 135 mg/m², which was the dose originally studied in ovarian cancer, to paclitaxel 250 mg/m². This comparison would demonstrate either a substantial difference between the two dose extremes or a lack of a clinically relevant dose response. For a variety of reasons, this comparison has not been performed. However, the question has broken into a number of smaller questions. It is uncertain whether a comparison of paclitaxel 210 to 250 mg/m² is really a clinically important question since the two doses are likely to be very close in terms of activity and toxicity. However, a comparison of paclitaxel 175 to 250 mg/m² is important. Paclitaxel 175 mg/m² is the FDA-approved dose, but is it the optimal paclitaxel dose? I do not think we know. Therefore, this three-arm study, because it compares the lowest and highest doses, will address a clinically relevant issue and give an important answer.

Outside of the clinical trial for metastatic breast cancer, we use paclitaxel 175 mg/m² by a three-hour infusion. However, based on our own data from the phase II trial using paclitaxel, we still use paclitaxel 250 mg/m² over 24 hours in the adjuvant population.

DR SLEDGE

It has always seemed logical that schedule differences might make a tremendous difference for the taxanes because of their phase specificity. However, it makes less sense that one would see a significant increase in response above a certain dose level.

DR HORTOBAGYI

It is important to think of the dose issue in conceptual terms. A dose response can be interpreted as a threshold dose below which there is less activity and above which there is more. It can be a simple threshold; I suspect that this is the case for many drugs in which intensification beyond a certain dose makes no difference in terms of efficacy. Alternatively, there are drugs for which an increase in dose is associated with an increase in response, response duration, or survival. Further, there is the issue of dose density, which differs from the amount of dose in a single administration and refers to the frequency and kinetics related to the frequency of administration. I think those three issues are entirely different and yet all relate to dose.

My bias, based on interpretation of the literature and my experience, is that there is clearly a dose response with the taxanes. I am not sure whether it is simply a threshold effect or whether there will be increasing yields with increasing dose, nor do I know what the shape of that dose-response correlation curve will be. Thus, I think it is important that we compare paclitaxel doses of 135, 175, 210, and 250 mg/m² and eventually compare much higher doses that can be administered with stem-cell support.

Clinical Experience With the Taxanes

DR HORTON

There are a number of ongoing clinical trials evaluating the taxanes in different patient groups. Are there any advantages for one taxane over the other in the clinical practice setting?

DR SLEDGE

To adequately answer this question, one must define the comparison. Are we comparing response rates, duration of treatment, or toxicity? I think we know or suspect that docetaxel has some toxicities that paclitaxel does not have. On the other hand, docetaxel probably has a higher overall response rate at its maximally tolerated dose of 100 mg/m², compared with the FDA-approved paclitaxel dose of 175 mg/m². Currently, there is only one ongoing clinical trial directly comparing paclitaxel with docetaxel in patients with metastatic breast cancer. A concern regarding this trial is that docetaxel 100 mg/m² is being compared with paclitaxel 175 mg/m², and these doses are not equitoxic.

Clearly, there are patients who can receive paclitaxel for prolonged periods. In the ECOG studies, a number of patients received 30 cycles of paclitaxel therapy. I suspect that we will not see many patients receiving 30 cycles of docetaxel. Again, this goes back to how we define the comparison. These are different agents, and therefore, we are probably going to find different clinical settings in which each can be beneficial to selected patients.
The only way to compare taxane schedules or one taxane with another is to use equitoxic dose schedules. For example, optimal paclitaxel scheduling was evaluated in a randomized trial (BMS71) in which women with metastatic breast cancer received paclitaxel 175 mg/m² infused over either three or 24 hours. Eligible patients included those who had received no prior chemotherapy, adjuvant chemotherapy only, or chemotherapy for metastatic disease with or without prior adjuvant therapy. Overall, there were no differences in cumulative response rates, median progression-free survival, or overall survival between the two groups. However, the toxicities reported in each arm made it apparent that the regimens were not equitoxic, with more grade 3/4 neutropenia reported in patients receiving the 24-hour infusion. Also important is that the subset of previously untreated patients appeared to have a better response when paclitaxel was administered over 24 hours, suggesting that the 24-hour infusion schedule is better for that group of patients. However, it appears that this study demonstrates that the more aggressive schedule associated with more toxicity was much better in this untreated group of patients. Patients who were heavily pretreated had the same response regardless of treatment schedule.

Building on this theme, clinical trials designed to compare the intrinsic antitumor efficacy of the various taxanes should use equitoxic regimens. However, an ongoing randomized phase III trial (RPR56976-311) designed to identify whether paclitaxel or docetaxel has superior activity in women with previously treated metastatic breast cancer does not use equitoxic regimens. Patients are randomized to receive either docetaxel 100 mg/m² (one-hour infusion) or paclitaxel 175 mg/m² (three-hour infusion). The paclitaxel dosing schedule used in this trial is significantly less aggressive in its potential to induce myelosuppression and possibly antitumor activity. A more apt comparison would have been to use a paclitaxel dose of 225 mg/m². Thus, this trial is unlikely to provide useful data regarding the comparative effects of these two agents.

**Duration of Therapy**

**DR HORTON**

I have some breast cancer patients who have received paclitaxel for one or two years and do not appear to develop major clinical resistance. How common is this phenomenon?

**DR SLEDGE**

In terms of therapy duration, only a small minority of patients are going to receive 20 to 30 cycles of paclitaxel. However, I think the very existence of that phenomenon raises the interesting biologic question of how paclitaxel works in these patients. We tend to think of drugs as working on tumors; however, the idea that the cell kinetics of tumor growth vs tumor kill are so finely balanced that stable disease can be maintained for 30 therapy cycles seems rather unlikely. In fact, we have laboratory evidence that paclitaxel has antiangiogenic activity in vitro, killing vascular endothelial cells. It is certainly possible that the antiangiogenic activity rather than the specific antitumor activity maintains patients in prolonged remission. I suspect that in the future, we are going to understand that the taxanes are not simple drugs, and we will have to apply them in very complex and interesting ways.

**DR HORTOBAGYI**

The issue of duration of therapy makes it even more important for us to define the optimal dose of these drugs. We know that toxicity is dose related for both taxanes. Therefore, chronic administration with lower rather than higher doses of either taxane should be more attractive in terms of toxicity. If patients who are going to have these long responses can be identified, ideally they could be treated with the minimal effective dose.

**DR SLEDGE**

The paclitaxel dose required to put a patient into remission (ie, the tumor-kill dose) is probably quite different from the dose required to destroy vascular endothelial cells. Therefore, if the antiangiogenic activity is indeed important in patients who are long-term responders or who have long-term stable disease with paclitaxel, then that dose may be 10% of the dose needed to kill the tumor cells.

**DR HORTON**

What is the optimal treatment duration for metastatic breast cancer?

**DR SLEDGE**

There have been five randomized trials of chemotherapy in metastatic disease using a variety of different regimens. None has shown a survival advantage for prolonged therapy duration or a clinically impressive difference in time to treatment failure. Only one study evaluated quality of life and demonstrated superior quality of life with prolonged therapy duration. We should revisit this issue with paclitaxel and docetaxel. In Eastern Cooperative Oncology Group studies, patients who had a partial remission or stable disease while receiving single-agent paclitaxel or paclitaxel-based regimens continued to receive paclitaxel until disease progression.

**DR HORTON**

Dr Hortobagyi, do you continue to treat patients who have a complete remission?

**DR HORTOBAGYI**

The majority of patients who obtain a complete remission eventually relapse. Thus, the duration of treatment relates to the patient's preference. Despite the inconvenience of continued treatment, many patients prefer a single, progression-free period rather than multiple reinduction periods. In general, I think this issue should be discussed individually with patients.

We have not made progress on the issue of therapy duration. The heterogeneity of breast cancer is such that some patients may attain optimal response with three treatment cycles, while others may not be adequately treated even after 12 cycles. Unfortunately, the majority of studies comparing shorter vs longer treatment regimens have included too few patients to answer the question. Further, this issue is probably as important for adjuvant therapy as for metastatic treatment. We have elected to arbitrarily pick an adjuvant treatment duration in this setting for reasons of convenience. However, we do not know what duration is optimal for each patient.

It may be advantageous to identify specific biologic characteristics that will allow us to test whether a longer or shorter therapy duration is better on a tumor-specific basis. For example, we could use a kinetic parameter, such as the S-phase fraction or doubling time. Alternatively, a particular molecular characteristic may be an effective identifying method to select patients who benefit from shorter or longer therapy duration.
Taxane Combinations

DR HORTON

Dr Sledge, you mentioned earlier that cardiac toxicity was observed in the Milan study with the doxorubicin/paclitaxel combination. How do you suggest using paclitaxel with doxorubicin in clinical practice?

DR SLEDGE

This is a crucial question regarding the use of this combination, particularly in the micrometastatic setting. We have always dealt with congestive cardiomyopathy in the metastatic setting, but the question becomes how many doses can be administered before the toxicity is observed. However, if we have a regimen with a 94% response rate and a 40% complete response rate in the metastatic setting and apply it to the micrometastatic setting where some patients are long-term disease-free survivors without any treatment, the question of toxicity becomes increasingly important.

The first question is whether the incidence of congestive cardiomyopathy with this regimen is significantly greater than that observed with standard regimens. In nonrandomized phase II studies, the incidence of symptomatic congestive heart failure following doxorubicin/paclitaxel ranged from 13% to 21%, depending on the cumulative doxorubicin dose and treatment regimen. Dr Hortobagyi's group also is currently evaluating this question. The Southwest Oncology Group (SWOG) has been looking at this in a randomized phase II trial comparing doxorubicin/paclitaxel to doxorubicin/cyclophosphamide. The ECOG is repeating the Gianni et al protocol using paclitaxel/doxorubicin in which we cap doxorubicin dose at 360 mg/m².

Together, these trials should give us a reasonable idea of whether it is safe to evaluate this regimen in a larger adjuvant trial. In the Intergroup setting, we are actively investigating the possibility of using a regimen similar to that used by Gianni et al for the upcoming adjuvant trials. I believe that this decision will be made in the near future.

DR HORTOBAGYI

Initial trials using this combination showed that there is a sequence-dependent interaction between the two agents and that the pharmacokinetics of doxorubicin can be altered by the preadministration of paclitaxel. This is not unique to this two-drug combination; a variety of two-drug combinations that contain taxanes display this sequence-dependent interaction. It is important to remember that those earlier trials for doxorubicin and paclitaxel did not report any significant cardiac toxicity.

Two recent studies evaluated the combination of doxorubicin and paclitaxel and paclitaxel and reported only a very high degree of activity, but also a 20% congestive heart failure rate and a somewhat higher rate of subclinical or scan-detected cardiac abnormalities. A number of additional studies with this combination are using similar schedules and doses. Although these studies are not as mature (suggesting a lower cumulative doxorubicin dose), a high degree of cardiac toxicity has not been observed.

There is a very interesting trial in which the same doses of doxorubicin and paclitaxel were used as in previous trials, but administration of doxorubicin and paclitaxel was separated by 16 hours. This administration schedule resulted in a high response rate without substantial cardiac toxicity. Although a small number of patients were enrolled, investigators observed a >30% complete remission rate, which is substantial. Finally, it is important to mention that a follow-up study by the Milan group is underway using the same regimen but capping the dose of doxorubicin at 360 mg/m². My group is evaluating a similar regimen; preliminary evidence suggests that limiting the total doxorubicin dose decreases the cardiac toxicity to the expected rate for any anthracycline-based regimen.

It is important to identify whether the excess cardiac toxicity observed with this combination in some studies is real and reproducible. If it is real, it is then important to learn the mechanism of the interaction. I believe that six doxorubicin/paclitaxel cycles are effective and safe. However, I am somewhat hesitant to unreservedly recommend this regimen to physicians in the community because we do not yet know the safety profile of long-term (ie, more than six cycles) doxorubicin/paclitaxel administration. Based on cardiac biopsies and MUGA scans performed at M.D. Anderson thus far, evidence suggests that total doxorubicin doses up to 360 mg/m² do not demonstrate excess subclinical cardiac toxicity compared with our experience with FAC or other anthracycline-based regimens. Therefore, I think it is important to dissect this issue, and the ongoing trials should provide greater insight into the reproducibility and mechanism of cardiac toxicity with this combination.

DR SLEDGE

This is an important issue because I think everyone who treats breast cancer believes that a regimen that is highly active in the overt metastatic setting presumably should improve the situation in the adjuvant setting. It is important that we move these active regimens to the adjuvant setting as quickly and as safely as possible.

With the original data using higher paclitaxel doses, one could make a case for single-agent paclitaxel being as effective as combinations in front-line therapy. However, I think paclitaxel 175 mg/m² over three hours demonstrates a somewhat lower activity rate than that of the most commonly used combinations. Therefore, combinations including paclitaxel and another commonly used agent may be a better choice.

DR ROWINSKY

It appears that paclitaxel reduces the clearance of doxorubicin and its metabolites by 30% to 35%. Thus, data from the Gianni trials demonstrate that doxorubicin 360 mg/m² can safely be administered with paclitaxel in combination in previously untreated patients with metastatic breast cancer. There have been claims that a higher cumulative doxorubicin dose can be administered with docetaxel. However, the phase I docetaxel/doxorubicin combination trials have been performed to date only in patients who do not receive a very high cumulative doxorubicin dose in combination. For example, the majority of patients received a substantial portion of their total doxorubicin dose in the adjuvant setting; therefore, only a few cycles of combination docetaxel/doxorubicin could be administered. In other words, few patients received their total cumulative doxorubicin dose of 480 mg/m² in combination with docetaxel. Therefore, an adequate comparison of these two regimens really cannot be made at this time because we have not yet treated a sufficient number of patients with docetaxel/doxorubicin in the same context in which Dr Gianni treated patients with paclitaxel/doxorubicin.

Management of Toxicities

DR HORTON

Do you have recommendations on specific methods to reduce the toxicity of the taxanes?
With regard to paclitaxel, different toxicities are related to different administration schedules. Clearly, a decrease in neutropenia is observed with a decrease in the infusion time from 24 to 3 hours. There is also preliminary evidence that shorter infusion times are associated with increased neurotoxicity. Thus, there are tradeoffs among different toxicities with paclitaxel. Efforts to decrease neurotoxicity have been suggested anecdotally. We have found pyridoxine (vitamin B₆) administration to be helpful. However, I am unaware of any randomized comparison evaluating different methods to decrease neurotoxicity.

**DR SLEDGE**

Anecdotally, we have observed virtually no neurotoxicity with the 96-hour paclitaxel infusion. In our doxorubicin/paclitaxel combination study (paclitaxel give over one or three hours), we extend the paclitaxel infusion to 96 hours if we administer more than six cycles and the patient is experiencing significant neurotoxicity. Using this strategy, we have been able to stop neurotoxicity progression and, in some cases, we have observed a reversal.

**Weekly Paclitaxel Administration**

**DR SLEDGE**

The weekly paclitaxel infusion schedule is attractive. The weekly schedule results in changes in the characteristics of this agent. First, one is able to administer much higher cumulative doses with the weekly schedule. There have been reports from several centers in which weekly administration of paclitaxel 80 to 175 mg/m²/week for 6 to 8 weeks is possible (Table 6). The total paclitaxel dose administered in that situation is two to three times the total dose administered with a three-week schedule, regardless of infusion rate. This can be achieved without excess myelosuppression. Other side effects also appear markedly decreased, including alopecia and hypersensitivity. This may be due to a substantially lower peak concentration after each individual dose or to some improved host tolerance of the weekly schedule.

Ongoing clinical trials will offer additional data on his promising administration schedule.

Table 6 -- Experience With Weekly Paclitaxel in Pretreated Advanced Malignancies

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor Type</th>
<th>Paclitaxel Regimen</th>
<th>Number of Evaluable Patients</th>
<th>OR (%)</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lotzher et al</td>
<td>Breast</td>
<td>90 mg/m² IV</td>
<td>6</td>
<td>50</td>
<td>Neutropenia; no hematologic toxicity observed</td>
</tr>
<tr>
<td>Ferenczy et al</td>
<td>Ovarian</td>
<td>40 to 100 mg/m² IV, 1-h infusion</td>
<td>18</td>
<td>30</td>
<td>No mucositis or grade 3 neurotoxicity; 1/78 pts developed alopecia</td>
</tr>
<tr>
<td>Akwariyi et al</td>
<td>NSCLC</td>
<td>100 to 200 mg/m² IV for 3 to 5 weeks</td>
<td>24</td>
<td>38</td>
<td>DLT: neutropenia, dermatologic, neurotoxicity (44: 200 mg/m²); mucositis/ neuropathy (2/5: 153 mg/m²)</td>
</tr>
<tr>
<td>Brestan et al</td>
<td>Multiple</td>
<td>80 mg/m² IV, 1-h infusion</td>
<td>12</td>
<td>NR</td>
<td>No grade 3 toxicity observed</td>
</tr>
<tr>
<td>Löffler et al</td>
<td>Multiple</td>
<td>40 to 90 mg/m² IV for 5 h</td>
<td>50</td>
<td>40</td>
<td>No grade 3 hematologic toxicity; no HSR; dermatologic, cardio toxicity observed</td>
</tr>
</tbody>
</table>

One other important issue related to the weekly schedule is that both taxanes are radiosensitizers, although this has been better studied with paclitaxel. Optimally, paclitaxel should be given by multiple divided doses in association with radiation therapy as opposed to a single administration in order to exploit its radiosensitizing effect. The weekly schedule is therefore ideal and is well tolerated.

**DR HORTOBAGYI**

The theoretical advantage of weekly paclitaxel is that the drug is very avidly bound to body tissues with measurable concentrations for approximately one week, after which time most of the drug is gone from body tissues. However, for three to five days, its concentration is very high in body tissues. Thus, weekly administration tends to replenish body stores. In my opinion, it is pharmacologically equivalent to paclitaxel continuous infusion. Many people believe that the only way to attain continuous exposure to a drug is by administering it as a continuous infusion. This can be achieved without excess myelosuppression. Other side effects also appear markedly decreased, including alopecia and hypersensitivity. This may be due to a substantially lower peak concentration after each individual dose or to some improved host tolerance of the weekly schedule.

Ongoing clinical trials will offer additional data on his promising administration schedule.

**DR ROWINSKY**

The theoretical advantage of weekly paclitaxel is that the drug is very avidly bound to body tissues with measurable concentrations for approximately one week, after which time most of the drug is gone from body tissues. However, for three to five days, its concentration is very high in body tissues. Thus, weekly administration tends to replenish body stores. In my opinion, it is pharmacologically equivalent to paclitaxel continuous infusion. Many people believe that the only way to attain continuous exposure to a drug is by administering it as a continuous infusion. This is not the case with paclitaxel, because the drug binds very admirably to body tissues sites, even when it cannot be measured in plasma.

**References**


Semin Oncol. 1997;24(suppl 3):S3-1-S3-3.


