In recent years, the clinical application of paclitaxel (Taxol), docetaxel (Taxotere), vinorelbine (Navelbine), and trastuzumab (Herceptin) has improved the management of advanced breast cancer. With the introduction of gemcitabine (Gemzar), a novel cytotoxic agent with unique modes of action and cross resistance, provides an important addition to the armamentarium for this disease.

In the late 1980s and early 1990s, investigators reported activity for gemcitabine in a variety of human tumor-cell lines and xenografts. In the early 1990s, as investigators at the Free University in Amsterdam were examining the basic mechanism of interaction between gemcitabine and cisplatin (Platinol) in cell line systems, our laboratory began evaluating gemcitabine in a broad array of human tumor primary culture specimens utilizing an ex vivo apoptotic model. Preliminary results indicated significant correlations between gemcitabine and cisplatin ($P < .05$) and gemcitabine and mustard alkylators ($P < .01$) by Pearson correlation. This finding led to the analysis of gemcitabine in combination with other classes of cytotoxic drugs. We reported synergy between gemcitabine and cisplatin in 73% of human tumor primary cultures and, more recently, synergy between mustard alkylators and gemcitabine in 69% of human tumor specimens. The degree of true synergy identified for cisplatin plus gemcitabine has exceeded that identified between any other classes of drugs evaluated by our laboratory to date.

Based on laboratory findings, we applied the gemcitabine/cisplatin combination in a number of tumor types, with particular attention to relapsed ovarian and breast cancers, two diseases with significant activity and synergy in the EVA (ex vivo apoptotic) assay. Preliminary results in ovarian cancer have been reported. In this article, we focus on the role of gemcitabine plus cisplatin in advanced breast cancer.

Scientific Rationale

Platinum Therapy in Breast Cancer

In 1978, a phase II trial of cisplatin in relapsed breast cancer provided no objective responses in 26 evaluable patients. This led to the virtual disappearance of cisplatin from the breast cancer literature for a decade. When cisplatin was subsequently tested in previously untreated advanced breast cancer patients, Sledge et al observed responses in 9 of 19 patients (47%), identifying it as one of the more active agents in this disease. Other investigators who compared the activity of cisplatin or carboplatin (Paraplatin) in previously treated vs chemotherapy-naive breast cancer patients have reported similar results. In a study reported by Jurga et al the 53.9% objective response rate for cisplatin in untreated breast cancer patients fell to 30.6% for relapsed patients.

A study of carboplatin as a single agent yielded a response rate of 35% in previously untreated breast cancer patients. However, when clinical trials compared carboplatin in previously
untreated vs previously treated patients, the objective response rates fell from 33% to 8% in one and 32% to 0% in the second study.[18,19] It is evident that platinum activity falls dramatically in previously treated populations, suggesting collateral resistance to this class of drugs induced by prior exposure to cytotoxics.

In the early 1990s, as the use of platinum in breast cancer gained acceptance, platinum-based combination therapies were shown to provide objective responses in a number of trials (Table 1). Accumulated experience indicates that platinum derivatives have activity in breast cancer, that platinum activity appears greater in chemotherapy-naive patients, and that some platinum-based combinations are highly effective in this disease.

**Gemcitabine Activity in Breast Cancer**

The activity of gemcitabine as a single agent for advanced breast cancer has been the subject of prior investigation with responses observed in approximately 20% of patients.[27-33] (Other studies, however, have shown efficacy rates varying from 25% to 46%, depending on starting dose and status of prior chemotherapy for metastatic disease.[34,35]) The principal toxicities associated with gemcitabine are generally mild to moderate in severity and include neutropenia, thrombocytopenia, malaise, and asthenia, with rash, dyspnea, alopecia, and nausea reported less frequently.

Gemcitabine’s favorable toxicity profile has led many investigators to suggest gemcitabine as an ideal agent for combination therapy.

The results of clinical trials of gemcitabine plus paclitaxel (Taxol),[36] docetaxel (Taxotere),[37] vinorelbine (Navelbine),[38] doxorubicin,[39] and epirubicin (Ellence),[40] as well as triple-agent regimens such as gemcitabine/epirubicin/paclitaxel (Taxol) (GET), have been reported.[41] Additional trials are underway to further evaluate gemcitabine’s role in this disease.

The question that arises from these trials remains: How do we optimize drug/drug interactions, based on mechanisms of action, to provide the most effective combination regimens? To address the question we examined gemcitabine’s activity in combination with a variety of cytotoxic agents and determined the degree of true synergy for each doublet (Figure 1).

As can be seen, cisplatin revealed the highest degree of synergy with gemcitabine. Our group reported a formal examination of the degree of activity and synergy for the combination of gemcitabine plus cisplatin (Table 2).[10] This analysis revealed activity and synergy for breast cancer, a disease not generally targeted for this combination.

To determine the objective response rate and assess the predictive validity of the ex vivo apoptotic predictions for this combination, we initiated a phase II trial of gemcitabine/cisplatin in relapsed breast cancer patients. To approximate the in vitro conditions, our design incorporated a repeating doublet sequence wherein both drugs are administered together each day of therapy. To date, three clinical trials combining cisplatin with gemcitabine in advanced breast cancer have been reported (Table 3).[42-44]

Hematologic toxicity has been the most commonly reported side effect with no treatment-related deaths noted in any of the studies. A more detailed review of the phase II trial reported by our group follows.

**Repeating Doublet Gemcitabine/Cisplatin**

Between May 1997 and October 1998, we conducted a phase II trial of low-dose cisplatin plus gemcitabine in a repeating doublet sequence in patients with previously treated, relapsed breast cancer. The original trial of cisplatin (30 mg/m^2) plus gemcitabine (1,000 mg/m^2) administered on days 1, 8, and 15 every 28 days was modified to cisplatin (30 mg/m^2) plus gemcitabine (750 mg/m^2) on days 1 and 8 every 21 days following the observation of day 15 myelosuppression.

**Patients and Methods**
All patients had received one or more prior chemotherapy regimens for systemic recurrence and all had Eastern Cooperative Oncology Group performance status \( \leq 3 \), with adequate bone marrow, hepatic, and renal function. Concurrent radiation or hormonal therapy was not allowed. Patients with clinically stable brain metastases or other sites of metastases who had completed radiation therapy were permitted. Patients were eligible regardless of the type of prior therapy, including high-dose therapy with stem-cell rescue, or prior exposure to cisplatin or gemcitabine, provided these two drugs were not given together. Patients with accessible sites of recurrence had tissue submitted for blinded ex vivo apoptotic laboratory analysis of sensitivity to gemcitabine plus cisplatin.\[45\] The results of the ex vivo apoptotic assay were not used in the selection of patients.

The primary end points of the trial were safety and efficacy measured as objective response rate and time to progression. A secondary end point was to compare ex vivo apoptotic assay results with clinical outcome. All patients signed written informed consents. Patients were tested for HER2 overexpression using anti-c-erbB2 mouse monoclonal IgG1.\[46\]

Statistical calculations were performed using SPSS (Statistical Package for the Social Sciences) version 7.5. Survival curves were generated using the Life table function. Comparisons were performed using the Wilcoxon (Gehan) test, which compared the following subgroups: HER2 (positive vs negative), assay (sensitive vs resistant), and number of prior treatments (1 to 2 vs > 3). Results were considered significant at the .05 level.

### Treatment Plan

The repeating doublet schedule of cisplatin/gemcitabine administered on days 1, 8, and 15 every 28 days was modified to days 1 and 8 every 21 days due to day 15 myelosupression, as mentioned earlier. This modification occurred after the accrual of patient 12. The schedules were otherwise identical and were administered as follows.

All patients received hydration with D5½NS (dextrose in 0.5% normal saline) at 200 mL over 1 hour. Patients were premedicated with IV granisetron (Kytril) at 1 mg and IV dexamethasone at 10 mg. Cisplatin at 30 mg/m\(^2\) was administered in 250 mL of normal saline with 12.5 g of mannitol and 1 g of MgSO4 over 1 hour. A second hydration with 250 mL of D5½NS over 1 hour was followed by gemcitabine at 750 mg/m\(^2\) in 250 mL of normal saline over 1 hour. Patients with two or more prior chemotherapy regimens were started at a gemcitabine dose of 600 mg/m\(^2\). All treatments were administered on an outpatient basis.

### Results

Between May 1997 and October 1998, 31 patients entered the study. One patient developed brain metastases at the second week and was considered not evaluable. The remaining 30 patients who received at least one cycle of therapy are included. There were 3 (10%) complete responses and 12 (40%) partial responses for an overall objective response rate of 50%. Two of four patients accrued following relapse from high-dose therapy with stem-cell support had objective responses. Responses were observed in soft tissue, lung, liver, and bone. No responses were observed in the central nervous system. Of the 30 patients, 8 developed central nervous system metastases, 6 of whom had objective systemic responses at the time of central nervous system relapse. Among responding patients (complete and partial responses), there was a median time to progression of 23.5 weeks, with a mean of 25 weeks.

Toxicity was primarily hematologic with grade 3 and 4 leukopenia in 13%, neutropenia in 10%, anemia in 4%, and thrombocytopenia in 31% of treatment cycles. The most frequent subjective side effect reported by 44% of the patients was mild-to-moderate fatigue; 36% of patients reported moderate nausea without vomiting. Overall, the regimen proved to be quite tolerable.

Of the 22 patients for whom tissue blocks were evaluable, 5 were positive and 17 negative for HER2 overexpression. This precluded analysis of the impact of HER2 overexpression on response to this combination. A comparison of a number of prior treatments (1 or 2 vs 3 or more) and time to progression (14 vs 22 weeks) did not achieve significance \((P < .32)\). However, ex vivo apoptotic assay sensitivity to the drug combination correlated significantly \((P < .03)\) with time to treatment.
Gemcitabine Plus Cisplatin in Breast Cancer

Published on Cancer Network (http://www.cancernetwork.com)

Discussion

Gemcitabine's Place in Combination Therapy

In a series of clinical trials, single-agent gemcitabine has provided objective responses in approximately 25% to 46% of patients with advanced breast cancer. The drug has a relatively mild toxicity profile, activity in solid tumors, and non-cross resistance with other classes of drugs.[47] Yet, it is gemcitabine's utility in combination therapy, specifically with cisplatin, that may hold the greatest clinical potential.

Resistance to cisplatin is primarily mediated by nucleotide excision repair[48] and mismatch repair.[49] After DNA platination, DNA polymerases incorporate nucleosides into sites of DNA damage. Evidence supporting the role of nucleotide excision repair in the synergy between cisplatin and gemcitabine has recently been provided. Using mismatch repair deficient cell lines, Yang has shown that antisense ERCC1 RNA abrogates the cytotoxic synergism between cisplatin and gemcitabine.[50]

To enhance difluorodeoxycytidine triphosphate (dFdCTP) incorporation, in keeping with in vitro observations, cisplatin/gemcitabine was administered in a repeating doublet sequence in two of the reported trials and as a 4-day cisplatin infusion with gemcitabine on days 2 and 8 in one trial. The rationale for the combination is the repeated induction of genomic insult followed by repair inhibition. Studies conducted in our laboratory have indicated that synergy persists for these drugs even at low cisplatin concentrations (ie, 1.65 mg/mL continuous exposures in fixed ratios with gemcitabine). Prior observations in the A2780 ovarian carcinoma cell line revealed that wild-type and cisplatin-resistant subclones were sensitive, yet gemcitabine-resistant subclones were resistant to the two-drug combination.[51] Cells with efficient DNA repair may be uniquely sensitive to agents that target excision repair processes.

Gemcitabine’s activity as an inhibitor of ribonucleotide reductase provides further pharmacokinetic advantages for this agent over the structurally related cytosine arabinoside and cisplatin (ara-C). The higher intracellular concentrations of dFdCTP over ara-CTP and its prolonged intracellular half-life may in part explain the superior activity of the gemcitabine/cisplatin doublet in breast cancer over the results obtained by the Cancer and Leukemia Group B in a clinical trial that combined cisplatin with ara-C.[51]

When we compared the ex vivo apoptotic results from previously treated vs previously untreated breast cancer specimens, we found comparable degrees of sensitivity and a trend toward greater sensitivity and synergy in the previously treated group. The objective responses observed in two of the four patients who had relapsed following high-dose therapy with stem-cell support in our series and the responses observed in the heavily pretreated patients in the other series indicates that prior treatment and the development of repair-mediated resistance does not preclude benefit from this combination.

Optimal Treatment Regimens

Optimal doses and schedules for the combination of cisplatin plus gemcitabine remain to be determined. A comparison of schedules in non-small-cell lung cancer suggested that day 15 cisplatin combined with day 1, 8, and 15 gemcitabine was superior to the schedule employed in this trial of breast cancer patients.[52] Our experience with repeating doublet schedules in this trial and in the treatment of advanced ovarian cancer[13] is consistent with prior in vitro and in vivo observations[53] and raises the question of whether optimal schedules may be disease-specific.

We observed no significant correlation between the number of prior treatment regimens, 1 or 2 vs 3 or more, and outcome ($P = .32$) for the doublet sequence. The 4-day cisplatin infusion schedule reported by Doroshow et al[43] revealed a trend favoring the minimally (zero or one regimen) over the heavily treated (two or more regimens) groups. In the two trials, all patients who used the
doublet sequence had failed one or more prior regimens for metastatic disease.

This finding raises several issues. First, patients who are minimally treated are more likely to respond to cisplatin, as we described earlier. The 4-day infusion schedule is cisplatin-intensive, providing 100 mg/m\(^2\) as opposed to the 50 or 60 mg/m\(^2\) in the other schedules. Second, two of the trials administered the drugs together as a doublet, optimizing drug-drug interaction, while the 4-day schedule only administered the two drugs together once on day 2.

Taken together, the close temporal sequencing of the two drugs in the repeating doublet schedule may hold certain advantages. The doublet schedule uses low-dose cisplatin to enhance gemcitabine incorporation and cytotoxicity. This is fundamentally different from the use of gemcitabine to enhance high-dose cisplatin cytotoxicity. In relapsed, previously treated and largely drug-refractory patients whose resistance may be largely mediated by efficient DNA repair capacity, the doublet sequence holds theoretical advantage. Further study will be required to determine optimal schedules of administration for these agents.

**Gemcitabine in Differing Combinations**

The role of other platinum derivatives for combination with gemcitabine is of interest. Our laboratory findings comparing carboplatin with cisplatin have revealed high degrees of concordance for these agents, suggesting that carboplatin interacts with gemcitabine in a manner similar to cisplatin[54]. Our choice of cisplatin reflected the greater degree of myelosuppression associated with carboplatin. However, appropriately dosed, carboplatin may be able to be safely used in place of low-dose cisplatin in a repeating doublet sequence in breast cancer, as was recently reported for this combination in non-small-cell lung cancer.[55] When we compared the degree of gemcitabine synergy with cisplatin to gemcitabine synergy with oxaliplatin, the incidence was identical at 73% for both drugs,[56] suggesting similar degrees of clinical activity for these combinations.

The clinical activity for the combination of cisplatin plus gemcitabine in relapsed breast cancer has been associated with manageable toxicity, primarily hematologic in the form of thrombocytopenia. In our series we observed responses in liver, lung, bone, and soft tissue sites, indicating activity for visceral recurrences. However, we observed no activity in patients with central nervous system disease, suggesting that this combination does not penetrate the blood-brain barrier adequately to provide central nervous system protection.

The correlation between ex vivo apoptotic assay and outcome in our study suggests that future studies might incorporate this or related techniques into trial design, or for the selection of treatment candidates, as described in a recent review.[57]

**Conclusion**

In summary, the combination of cisplatin plus gemcitabine is active in relapsed breast cancer patients. The activity observed in drug-resistant patients, even following high-dose/stem-cell therapy, suggests relative non-cross resistance with other drug combinations. Future trials incorporating this combination into earlier stages of the disease and for consolidation strategies are warranted.

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