Gemcitabine Plus Cisplatin Repeating Doublet Therapy in Previously Treated, Relapsed Breast Cancer Patients

By Robert A. Nagourney, John S. Link, Jonathan B. Blitzer, Cynthia Forsthoff, and Steven S. Evans

Purpose: **To determine the safety and efficacy of gemcitabine plus cisplatin for patients with relapsed adenocarcinoma of the breast.**

Patients and Methods: **Previously treated patients with adenocarcinoma of the breast received cisplatin (30 mg/m^2) plus gemcitabine (1,000 mg/m^2) on days 1, 8, and 15 of each 28-day cycle, which was changed after patient no. 12 to cisplatin (30 mg/m^2) plus gemcitabine (750 mg/m^2) days 1 and 8 of each 21-day cycle.**

Results: **Of 30 patients, three (10%) had complete and 12 (40%) had partial responses, for an overall response rate of 50%. Two objective responses were observed among the four patients accrued after relapse that followed high-dose/stem-cell therapies. The median time to progression was 14 weeks. The median time to progression for objective responders was 23.5 weeks, with a range of 8 to 68 weeks. Toxicities included grades III and IV neutropenia in 13%, anemia in 6%, thrombocytopenia in 31%, grade III nausea in 4%, and grade II peripheral neuropathy in 2% of 151 treatment cycles. Moderate alopecia occurred in four patients. There were no treatment-related deaths.**

Conclusion: **Cisplatin plus gemcitabine is active and tolerable for patients with relapsed breast cancer. Responses observed in previously treated patients, including high-dose/stem-cell failures, indicate activity in otherwise drug-refractory patients.**

J Clin Oncol 18:2245-2249.

GEMCITABINE (2′,2′-difluorodeoxycytidine; dFdC) is a cytotoxic nucleoside analog, which differs from other fluoropyrimidines by the fluorine substitution on the ribose ring in a geminal configuration. The parent compound is sequentially phosphorylated by deoxycytidine kinase to the gemcitabine triphosphate dFdCTP,[1] which is incorporated into DNA, causing masked chain termination.[2] In addition, the diphosphate dFdCDP functions to diminish intracellular deoxynucleoside pools through the inhibition of ribonucleotide reductase.[3] Gemcitabine has in vitro activity against a broad array of human tumor cell lines[4] and has provided objective responses in a variety of human solid tumors.[5]

Cisplatin (*cis*-diaminedichloroplatinum [II]) is among the most widely used antineoplastic drugs with broad clinical activity. Although cisplatin has not been extensively applied in the United States in the first-line treatment of breast cancer, it has been shown to provide high objective response rates when used as initial therapy for this disease.[6] The degree of synergy between cisplatin and cytarabine identified in prior investigations[7,8] has also been found for the combination of cisplatin and gemcitabine.[9] Although the clinical potential of this combination continues to be investigated, its success in the treatment of non–small-cell lung cancer[10] recently led to the approval of the Food and Drug Administration for this indication.

In 1993, our laboratory began the systematic evaluation of gemcitabine (the kind gift of Dr Peter Tarassoff, Eli Lilly Company) in human tumor primary cultures.[11] The degree of synergy between cisplatin and gemcitabine reported in human cell lines[9,12] closely paralleled our findings in human tumor primary cultures, in which 73% (179 of 225) of the overall tumor specimens and 88% (21 of 24) of the breast cancer specimens revealed true synergy.[13,14] Prior mechanistic analyses had indicated that simultaneous or close temporal sequencing of gemcitabine and cisplatin exposures optimized the interaction.[12] Furthermore, the concentration ranges examined in our laboratory predicted that the serum concentrations of cisplatin achieved with low-dose administration schedules would be expected to retain the favorable pharmacologic effects in vivo. Based on these findings, a phase II trial of low-dose cisplatin plus gemcitabine in a repeating doublet sequence was initiated 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 of each 28-day cycle was modified to cisplatin (30 mg/m^2) plus gemcitabine (750 mg/m^2) on days 1 and 8 of each 21-day cycle after the observation on day 15 of myelosuppression (primarily thrombocytopenia) in several of the first 12 patients accrued.

From Rational Therapeutics, Inc, Long Beach Memorial Medical Center, and Memorial Breast Center, Long Beach, CA.

Submitted August 20, 1999; accepted February 15, 2000.

Supported in part by Eli Lilly Company, Indianapolis, IN.

Presented in part at the Thirty-Fifth Annual Meeting of the American Society of Clinical Oncology, Atlanta, GA, May 15-18, 1999.

Address reprint requests to Robert A. Nagourney, MD, 750 East 29th Street, Long Beach, CA 90806; email RANAGOURNEY@RATIONALTHERAPEUTICS.COM.

0732-183X/00/1811-2245

PATIENTS AND METHODS

Eligible patients had measurable or assessable histologically confirmed breast carcinoma that had progressed after at least one prior chemotherapy regimen for systemic recurrence. All patients had Eastern Cooperative Oncology Group performance status of ≥ 3, with adequate bone marrow, hepatic, and renal function. Inclusion criteria were as follows: absolute neutrophil count of $\geq 1{,}000 \times 10^9$ cells/L, platelet count of $\geq 100{,}000 \times 10^9$ cells/L, creatinine level less than 2.0 mg/dL, bilirubin level less than two times normal, and the absence of active infection, clinical congestive heart failure, hypoxemia, and second malignancy within 5 years. Concurrent radiation or hormonal therapy was not allowed; however, patients with clinically stable metastases of the brain or other sites who had completed radiation therapy were permitted. Patients were eligible regardless of the nature of prior therapy, including high-dose therapy with stem-cell rescue and prior exposure to cisplatin or gemcitabine, provided that the two drugs were not given together. When possible, patients with accessible sites of recurrence, including pleural effusions, ascites, cutaneous metastases, and palpable lymph adenopathy, had tissue submitted for blinded ex vivo laboratory analysis of sensitivity to gemcitabine plus cisplatin. The results of ex vivo analyses were withheld from consideration until completion of therapy and were not used in the selection of patients for the trial. The primary end points of the trial were the safety of the therapy and its efficacy, which were measured as objective response rate and time to progression, with a secondary end point that compared ex vivo drug sensitivity with clinical outcome. All patients were provided a thorough explanation of the study, and all patients provided written informed consent. The study was approved by the sponsoring organization, Eli Lilly Company, Indianapolis, IN, and by the Western Institutional Review Board.

The ex vivo analyses of sensitivity to gemcitabine plus cisplatin were conducted on fresh specimens of tumor submitted to the laboratory as previously described.[15] Treating physicians were blinded to the results of the analyses until completion of therapy. The detection of HER-2 overexpression was conducted using anti–c-*erbB*-2 mouse monoclonal immunoglobulin G1, as previously described, with results scored from 1+ to 4+ with the anti-c-*erbB*-2 Detection Kit (Ventana Medical Systems, Inc, Tucson, AZ).

Statistical calculations were performed using SPSS software, version 7.5 (SPSS, Inc, Chicago, IL). Survival curves were generated using the life-table function. Comparisons were performed using the Wilcoxon (Gehan) test, which compared the following subgroups: HER-2 (positive *v* negative), assay (sensitive *v* resistant), number of prior treatments (one or two $v \geq$ three). Results were considered significant at the $P = .05$.

Treatment Plan

The repeating doublet schedule of cisplatin plus gemcitabine was initially administered on days 1, 8, and 15 of each 28-day cycle. In this group of previously treated breast cancer patients, cytopenias that occurred on day 15, primarily thrombocytopenia, led to a modification of the protocol after the accrual of patient no. 12 to a schedule of days 1 and 8 of each 21-day cycle. Both schedules were otherwise identical and were administered as follows.

All patients received hydration with D51/2 normal saline (NS) at 200 mL over 1 hour. Patients were premedicated with granisetron (Kytril; SmithKline Beecham, Philadelphia, PA) 1 mg intravenously and dexamethasone 10 mg intravenously. Cisplatin at 30 mg/m^2 was administered in 250 mL of NS with 12.5 g of mannitol and 1 g of $MgSO_4$, over 1 hour. Posthydration with 250 mL D51/2 NS over 1 hour was followed by gemcitabine at 750 mg/m^2 in 250 mL NS over 1 hour. Patients who had received 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

Thirty-one patients entered the study between May 1997 and October 1998. Baseline characteristics for the participants are listed in Table 1. One patient developed clinical evidence of brain metastases at the second week and was disqualified from formal evaluation. The remaining 30 patients, who received at least one cycle of therapy, are included in the analysis. The objective response rates for the 30 patients are provided in Table 2. Responses were observed in soft tissue, lung, liver, and bone. No responses were observed in the CNS, with eight of the 30 patients failing in this site and with six of these eight having objective systemic responses at the time of CNS relapse. Among responding patients (complete and partial responders), the times to progression were a median of 23.5 weeks and a mean of 25 weeks.

Toxicity was primarily hematologic (Table 3). Data on overall survival are provided in Fig 1. Of 22 patients for whom tissue blocks were assessable, five were found positive and 17 negative for HER-2 overexpression. An analysis of outcome by the number of prior treatment regimens (one or two $v \geq$ three) was conducted. These data are included in Table 4. A comparison between time to treatment progression and ex vivo sensitivity to the combination of cisplatin plus gemcitabine for the 12 patients for whom tissue was provided is reported in Fig 2.

DISCUSSION

The management of advanced and recurrent breast cancer continues to evolve. Single-agent gemcitabine has provided objective responses in approximately 20% of patients in a series of four clinical trials in advanced breast cancer.[16-19] The drug's mild toxicity profile, activity in solid tumors, and relative non–cross-resistance with other classes of drugs[20] offer opportunity for study. Gemcitabine's utility in combination therapy, specifically with cisplatin, may hold the greatest clinical potential.

The laboratory and clinical finding of activity for this combination in a previously treated patient with drug-refractory, advanced ovarian cancer provided the rationale for a clinical study of gemcitabine and cisplatin in ovarian cancer, preliminary results of which have been reported.[21] The observation that activity for cisplatin plus gemcitabine extended to a variety of human tumors in primary culture, including breast cancers,[13] suggested a treatment strategy applicable to diseases not generally targeted for the combination. Resistance to cisplatin seems to be primarily medi-

Table 1. Patient Characteristics

Patient No.	Age (years)	No. of Prior Treatments	Regimen	XRT	Site of Disease
1	37	3	CA, NOV/NVB, TXT	No	Bone, liver
2	53	3	CAF, BMT, 5-FU	Yes	Bone, lung
3	58	3	CMF, NVB, TAX	No	Bone
4	70	3	MITO-C/NOV, TAX, NVB	No	Soft tissue, bone
5	74	1	CMF	No	Soft tissue, bone
6	60	5	CAF/MTX, TAX, NVB, 5-FU, TAX	No	Liver, lung, bone
7	43	2	CA, TAX	Yes	Bone
8	63	2	NVB, CMF	No	Soft tissue, bone
9	76	3	NVB, 5-FU, TAX	No	Lung, bone
10	66	1	TAX	Yes	Lung, bone
11	71	3	NVB, TAX, CMF	Yes	Lung, bone, liver
12	57	3	TAX, ADR, NOV	No	Liver
13	42	4	CA, TAX, NVB, MTX	Yes	Brain, bone, soft tissue
14	56	1	TAX	No	Bone
15	67	1	CAF	No	Soft tissue, bone
16	37	1	TAX	Yes	Bone
17	48	4	TAX, TAX/ADR, CAF, CA	No	Lung, soft tissue
18	66	1	CA	Yes	Bone, lung, soft tissue
19	46	1	TAX	Yes	Bone
20	67	3	CTX/5-FU, NVB, TAX	Yes	Bone
21	48	3	BMT, TAX, NVB	No	Lung, liver
22	50	2	NVB, CMF	No	Lung, bone
23	44	1	Ukrain*	Yes	Lung
24	55	3	TAX, NVB, TXT	No	Lung, bone
25	54	1	ADR	No	Lung, bone
26	49	5	CAF, CMF, BMT, TAX, PP/VP16	No	Soft tissue
27	72	2	TAX, CA	No	Lung
28	49	3	TAX, CA, BMT	Yes	Soft tissue
29	38	2	CA, TAX	Yes	Bone, lung, soft tissue
30	47	4	CA, IFX/ADR, Interferon, IL-2	Yes	Bone

Abbreviations: ADR, doxorubicin; BMT, bone marrow transplantation; CA, cyclophosphamide/doxorubicin; CAF, cyclophosphamide/doxorubicin/fluorouracil; CMF, cyclophosphamide/methotrexate/fluorouracil; CTX, cyclophosphamide; 5-FU, fluorouracil; IFX, ifosfamide; IL-2, interleukin-2; MITO-C, mitomycin-C; MTX, methotrexate; NOV, mitoxantrone; NVB, vinorelbine; PP, carboplatin; TAX, paclitaxel; TXT, docetaxel; VP16, etoposide; XRT, radiation therapy.

*J.W. Nowicky Pharmaceuticals, Vienna, Austria.

ated by nucleotide excision repair[22] and mismatch repair.[23] After DNA platination, DNA polymerases rapidly incorporate nucleosides into sites of DNA damage. To enhance the degree of dFdCTP incorporation, in keeping with in vitro observations, cisplatin and gemcitabine were administered in a repeating doublet sequence such that both drugs were given each day of therapy. The rationale was based on the repeated induction of genomic insult followed by repair inhibition, as had been reported previously.[12] Concentration-range studies conducted in our laboratory indicated that synergy persisted at successively lower cisplatin concentrations (ie, 13.2 to 1.65 ìg/mL continuous exposures in fixed ratios with gemcitabine). Prior observations in the A2780 ovarian carcinoma cell line had revealed that the wild-type and cisplatin-resistant subclones were sensitive, whereas gemcitabine-resistant subclones remained resistant to the two-drug combination.[12] Cells with efficient DNA repair may be uniquely sensitive to agents that target excision repair processes. A comparison of ex vivo results from previously treated versus previously untreated breast cancer specimens in our study revealed comparable degrees of sensitivity, ex vivo, with a trend toward greater sensitivity and synergy in the previously treated group. Although the sample size is small, the observation of objective responses

Table 2. Patient Responses (N = 30)

Type of Response	No. of Patients	%
CR	3	10
PR	12	40
SD	11	36
DP	4	13

NOTE. There were 20 measurable patients and 10 assessable.

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; DP, disease progression.

Table 3. Toxicities (N = 151 cycles)

Toxicity	Grade (no. of cycles) II	III	IV	III and IV	Total %
WBC count	80	17	2	19	13
ANC	42	11	4	15	10
HgB level	144	6	0	6	4
PLT count	32	33	14	47	31
N/V	0	6	0		4
Peripheral neuropathy	4	0	0		3
Alopecia	4	0	0		3

Abbreviations: ANC, absolute neutrophil count; HgB, hemoglobin; PLT, platelet; N/V, nausea/vomiting.

Table 4. Statistics

Variable	No. of Patients	Median Survival Time (weeks)	*P*	Time to Progression (weeks)	*P*
Overall	30	46		14	
No. of prior treatments					
1 or 2	11	54	< .17	22	< .32
> 3	19	41		14	
Assay status					
Sensitive	6	62	< .49	36	< .03
Resistant	6	43		15	

in two of four patients who had relapsed after high-dose/stem-cell therapies supports the study of the combination in this patient population.

The current report indicates clinical activity for the combination of cisplatin plus gemcitabine in relapsed breast cancer. Toxicity, primarily hematologic in the form of thrombocytopenia, was manageable with scheduled dose reductions. A comparison of response rates in the patients who received the days 1 and 8 schedule versus the days 1, 8, and 15 schedule revealed no differences. Responses in liver, lung, bone, and soft tissue sites indicate activity for visceral recurrences. The lack of activity in patients with CNS disease and the development of clinically significant brain and leptomeningeal recurrences in patients who enjoyed otherwise good systemic responses suggest that this combination does not adequately penetrate the blood-brain barrier to provide CNS protection.

Although a response rate of 50% was observed, the treatment was not curative. In this light, toxicity with regard to quality of life is important. The most common subjective treatment-related side effect, reported by 44% of the patients, was mild to moderate fatigue. This was followed by moderate nausea without vomiting in 36% of the patients. On questioning, 42% of the patients described having emotional distress, such as fear, nervousness, or anxiety, which they attributed to the disease recurrence and not to the specific treatment administered. Overall, the regimen proved to be tolerable.

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 cisplatin on day 2 or day 15 combined with gemcitabine on days 1, 8, and 15 or days 1 and 15 was superior to the schedule used in this trial of breast cancer patients.[24] Our experience with repeating doublet schedules in this trial and in the treatment of advanced ovarian cancer[21] is consistent with prior in vitro and in vivo observations[25] and raises the question of whether optimal schedules may be disease-specific.

In this trial, only five of 22 assessable patients exhibited HER-2 overexpression by immunohistochemistry. This small sample size precluded formal analysis of impact of HER-2 overexpression on outcome. The number of prior treatment regimens, one or two versus three or more on outcome, did not achieve significance ($P = .32$). However, among those patients for whom ex vivo laboratory analyses were conducted, there was a significant difference between drug-resistant patients and drug-sensitive patients with regard to time to progression. Median time to progression and median overall survival times were 36 and 62 weeks among patients who were found to be sensitive ex vivo and 15 weeks ($P = .03$) and 43 weeks among those who were

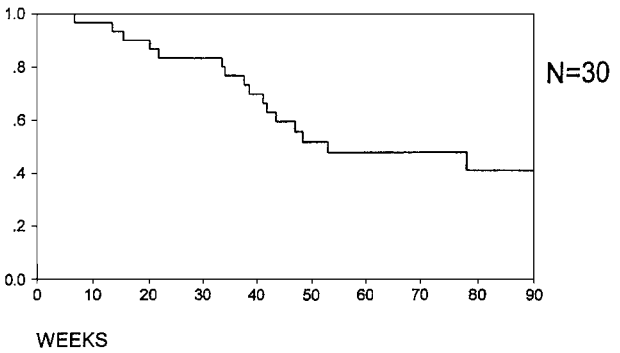

Fig 1. Survival.

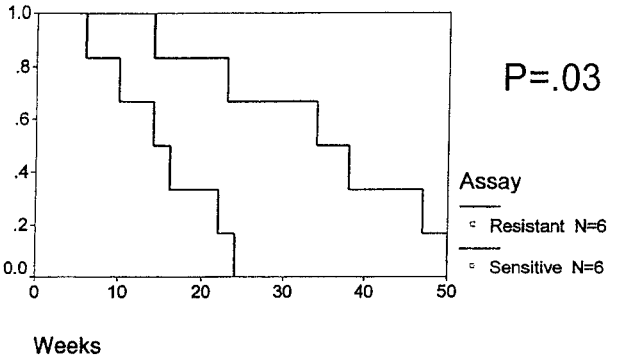

Fig 2. Time to progression.

assay-resistant, respectively. The latter did not achieve significance ($P = .49$). This finding is similar to prior observations in small-cell lung cancer wherein a survival advantage ($P = .035$) was observed in the assay drug-sensitive group.[26] The laboratory-based selection of breast cancer as a target for cisplatin plus gemcitabine in this study suggests that future studies might incorporate this technique or related techniques into trial design or for the selection of treatment candidates, as was described in a recent review.[27]

In summary, the combination of cisplatin plus gemcitabine administered in a repeating doublet schedule is active in relapsed breast cancer patients. The activity observed in drug-resistant patients, even after high-dose/stem-cell therapy, suggests relative non–cross-resistance with other drug combinations. Future trials are warranted that use this combination with earlier stage disease and incorporate consideration of its inclusion into consolidation strategies.

ACKNOWLEDGMENT

We thank Linda Kunkel, Barbara Sommers, Marianne Whisenhunt, Maxine Johnson, Michele Wright, Toni Espinoza-Ferrel, and Sue Harper for their assistance in patient care, statistical analysis, data management, and manuscript preparation.

REFERENCES

1. Heinemann V, Hertel LW, Gindley GB, et al: Comparison of the cellular pharmacokinetics and toxicity of 2′2′difluorodexycytidine and 1-b-D-arabinofuranosylcytosine. Cancer Res 48:4024-4031, 1988

2. Guchelar HJ, Richel DJ, Van Knapen A: Clinical, toxicological and pharmacological aspects of gemcitabine. Cancer Treat Rev 222: 15-31, 1996

3. Huang P, Chubb S, Hertel L, et al: Action of 2′2′ difluorodexycytidine on DNA synthesis. Cancer Res 51:6110-6117, 1991

4. Boven E, Schipper H, Erkelens CAM, et al: The influence of the schedule and the dose of gemcitabine on the anti-tumor efficacy in experimental human cancers. Br J Cancer 68:52-56, 1993

5. Carmichael J: The role of gemcitabine in the treatment of other tumours. Br J Cancer 78:21-25, 1998 (suppl 3)

6. Sledge GW Jr, Loehrer PJ Sr, Roth BJ, et al: Cisplatin as first-line therapy for metastatic breast cancer. J Clin Oncol 6:1811-1814, 1988

7. Fram RJ, Robichaud N, Bishov SD, et al: Interactions of *cis*-diamminedichloroplatinum(II) with 1-beta-D-arabinofuranosylcytosine in LoVo colon carcinoma cells. Cancer Res 47:3360-3365, 1987

8. Kyriazis AP, Kyriazis AA, Yagoda A: Enhanced therapeutic effect of *cis*-diamminedichloroplatinum(II) against nude mouse grown human pancreatic adenocarcinoma when combined with 1-beta-D-arabinofuranosylcytosine and caffeine. Cancer Res 45:6083-6087, 1985

9. Bergman AM, Ruiz van Helperen VWT, Veerman G, et al: Synergistic interactions between cisplatin (C-Pt) and gemcitabine (dfdc) in ovarian and colon cancer cell lines, in Sahota A, Taylor M (eds): Purine and Pyrimidine Metabolism in Man VIII. New York, NY, Plenum, 1995, pp 139-143

10. Cardenal F, Lopez-Cabrerizo MP, Anton A, et al: Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced non–small-cell lung cancer. J Clin Oncol 17:12-18, 1999

11. Nagourney R, Evans S, Makalinao A, et al: Gemcitabine activity in primary cultures of human cancer. Proc Am Assoc Cancer Res 37:318, 1996 (abstr 2161)

12. Peters GJ, Bergman AM, Ruiz van Haperen VW, et al: Interaction between cisplatin and gemcitabine in vitro and in vivo. Semin Oncol 22:72-79, 1995 (suppl 11)

13. Nagourney R, Su Y, Link J, et al: Gemcitabine synergy with cisplatin: Clinical and laboratory correlates. Proc Am Assoc Cancer Res 39:310, 1998 (abstr 2118)

14. Chou TC, Talahay P: Applications of the median-effect principle for the assessment of low-dose risk of carcinogens and for the quantitation of synergism and antagonism of chemotherapeutic agents, in Harrap KR, Connors TA (eds): New Avenues in Developmental Cancer Chemotherapy. New York, NY, Academic, 1987, pp 37-64

15. Nagourney RA, Evans SS, Messenger JC, et al: 2 chlorodeoxyadenosine activity and cross resistance patterns in primary cultures of human hematologic neoplasms. Br J Cancer 67:10-14, 1993

16. Carmichael J, Possinger K, Phillip P, et al: Advanced breast cancer: A phase II trial with gemcitabine. J Clin Oncol 13:2731-2736, 1995

17. Possinger K, Kaufmann M, Coleman R, et al: Phase II study of gemcitabine as first-line chemotherapy in patients with advanced or metastatic breast cancer. Anticancer Drugs 10:155-162, 1999

18. Blackstein M, Vogel CL, Ambinder R, et al: Phase II study of gemcitabine in patients with metastatic breast cancer. Proc Am Soc Clin Oncol 15:135a, 1996 (abstr 135)

19. Speilmann M, Llombart-Cussac A, Kalla S, et al: Single-agent gemcitabine is active in previously treated metastatic breast cancer (MBC). Ann Oncol (in press)

20. Waud WR, Gilbert KS, Gindley GB, et al: Lack of cross-resistance with gemcitabine against drug-resistant murine P388 leukemias. Cancer Chemother Pharmacol 38:178-180, 1996

21. Kunkel L, Evans S, Dottino P, et al: Cisplatin (CDDP) & Gemcitabine (dfdc) in relapsed ovarian cancer. Proc Am Soc Clin Oncol 17:357a, 1998 (abstr 1379)

22. Reed E: Platinum-DNA adduct, nucleotide excision repair and platinum based anti-cancer chemotherapy. Cancer Treat Rev 24:331-344, 1998 (review)

23. Vaisman A, Varchenko M, Umar A, et al: The role of hMLH1, hMLH3, and hMSH6 defects in cisplatin and oxaliplatin resistance: Correlation with replicative bypass of platinum-DNA adducts. Cancer Res 58:3579-3585, 1998

24. Shepherd F, Anglin G, Abratt R, et al: Influence of gemcitabine (GEM) and cisplatin (CP) schedule on response and survival in advanced non–small cell lung cancer (nsclc). Proc Am Soc Clin Oncol 17:472a, 1998 (abstr 1816)

25. Braakhuis BJ, Ruiz van Haperen VW, Welters MJ, et al: Schedule-dependent therapeutic efficacy of the combination of gemcitabine and cisplatin in head and neck cancer xenografts. Eur J Cancer 31A:2335-2340, 1995

26. Cortazar P, Gazdar AF, Woods E, et al: Survival of patients with limited-stage small cell lung cancer treated with individualized chemotherapy selected by in vitro drug sensitivity testing. Clin Cancer Res 3:741-747, 1997

27. Cortazar P, Johnson BE: Review of the efficacy of individualized chemotherapy selected by in vitro drug sensitivity testing for patients with cancer. J Clin Oncol 17:1625-1631, 1999