Carboplatin plus Gemcitabine Repeating Doublet Therapy in Recurrent Breast Cancer

Robert A. Nagourney,[1,2] Marshall Flam,[3] John Link,[4] Steven Hager,[5] Jonathan Blitzer,[6] William Lyons,[6] Barbara L. Sommers,[1] Steven Evans[1]

Abstract

Purpose: The combination of cisplatin plus gemcitabine is active in metastatic breast cancer. Carboplatin plus gemcitabine, widely used in ovarian and non–small-cell lung cancers, has also been used in breast cancer. This trial examined the efficacy and toxicity of split-dose carboplatin plus gemcitabine in advanced breast cancer. **Patients and Methods:** Patients with measurable disease, recurrent after adjuvant and ≤ 1 previous treatment for systemic disease, received carboplatin area under the curve = 2.0 (Calvert) plus gemcitabine 800 mg/m^2, both drugs administered days 1 and 8 every 21 days. Of 15 patients accrued, 13 are fully evaluable. **Results:** There were 2 complete (13.3%) and 6 partial (40%) responses, for an overall response rate by intention to treat of 53.3% (95% CI, 28%-82%). The median time to progression was 4.5 months (95% CI, 2.03-6.97 months), and median overall survival was 28.8 months (95% CI, 9.4-48.2 months). There were 2 patients with grade 3 (13.3%) anemia, 7 patients with grade 3 (46.6%) and 4 patients (26.6%) with grade 4 neutropenia, 4 patients with grade 3 (26.6%) and 3 patients (20%) with grade 4 thrombocytopenia. **Conclusion:** The repeating doublet of split-dose carboplatin plus gemcitabine reveals activity comparable to that of cisplatin plus gemcitabine, is well tolerated, and warrants evaluation in patients with recurrent breast cancer.

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Introduction

In recent years, there has been substantive progress in the management of breast cancer. Earlier detection, the introduction of new drugs, identification of novel targets, and improved supportive care have contributed to unprecedented survival for early-stage disease. Despite these advances, progress for patients with metastatic disease, extensive nodal involvement, or recurrence after initial therapy has been slow. The 5-year survival rate of 26% for patients with metastatic disease has not changed significantly in several decades.[1] A number of strategies have been used to address the needs of these patients. Although dose-intensive therapy with autologous marrow support have not improved outcomes, dose-dense schedules[2] have provided benefit in the adjuvant setting and are now more widely used. The introduction of new classes of drugs offers further hope to patients with advanced disease.

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Among the newer agents for breast cancer are capecitabine, pegylated liposomal doxorubicin, paclitaxel, docetaxel, albumin-bound paclitaxel, vinorelbine, and gemcitabine. As our understanding of drug actions improve, so does our appreciation of drug scheduling, sequence dependence, and synergy. The docetaxel/capecitabine doublet was conceived, in part, to upregulate thymidine phosphorylase and selectively deliver 5-fluorouracil to tumors.[3] We, and others, have explored the gemcitabine/platinum doublet to exploit the synergy between these agents in recurrent[4-9] and newly diagnosed breast cancer.[10,11] As platinum injury upregulates nucleotide excision repair (NER), gemcitabine triphosphate is avidly incorporated by repair-efficient cells, while gemcitabine diphosphate depletes cells of deoxynucleosides via the inhibition of ribonucleotide reductase.[12] Our original trial used a repeating doublet of cisplatin plus gemcitabine, with both drugs administered on days 1 and 8 every 21 days. The overall response rate (ORR) of 50% and median progression-free survival of 6 months in a heavily pretreated cohort supported the combination's role in advanced breast cancer.[13] A subsequent study of carboplatin area under the curve (AUC) = 4.5 (Calvert) day 1 plus gemcitabine at 1000 mg/m^2 days 1 and 8 every 21 days provided a partial response (PR) rate of 33% and median time to progression (TTP) of 20.5 weeks.[14] More recently, a trial of carboplatin

AUC = 4.0 day 1 plus gemcitabine at 1000 mg/m^2 days 1 and 8 provided an ORR of 31% and median TTP of 4.9 months.[15] We undertook this study in patients with previously treated, relapsed breast cancer to evaluate a split-dose carboplatin-based doublet that mimicked the original repeating doublet cisplatin-based schedule. The carboplatin dose of AUC = 2.0 was selected to approximate the 30 mg/m^2 cisplatin dose used in our original trial.[13]

Patients and Methods

Between January 2002 and December 2005, 15 patients were accrued. Patients received carboplatin AUC = 2.0 plus gemcitabine 800 mg/m^2, both drugs administered days 1 and 8 every 21 days. All patients had histologically confirmed breast cancer and had received adjuvant and ≤ 1 previous treatment for systemic relapse before accrual to the trial. All patients had bidimensional, measurable disease; Zubrod performance status 0/1; a white blood cell count > 2500/mm^3; absolute neutrophil count > 1500/mm^3; platelet count > 100,000/mm^3; hemoglobin > 10 g/dL; and normal liver, renal, pulmonary, and cardiac functions. Patients could have no clinical evidence of psychiatric disease, brain metastases, or other malignancy within the preceding 5 years. Patients could not have received radiation or chemotherapy within 1 month of accrual to trial. Patients remained on therapy until achievement of complete remission, disease progression, or until toxicity prevented continuation of therapy. A 2-stage sampling design was used by which a response rate of < 10% was considered of no clinical benefit, while a response rate of 30% warranted further clinical evaluation. Denoting $H_0 = 0.1$ and $H_a = 0.3$, if 3 of 25 responded, we would reject H_a, and if 7 of 25 or more responded, we would reject H_0 ($\alpha = 0.05$, $\beta = 0.1$). All patients signed informed consent.

Table 1 Patient Response to the Study Treatment

Response (%)	Number of Patients (N = 15; Intent to Treat)	Number of Patients (N = 13; Evaluable)
Complete Response	2 (13.3)	2 (15.4)
Partial Response	6 (40)	6 (46.2)
Overall Response Rate	8 (53.3)	8 (61.6)
Stable Disease	2 (13.3)	2 (15.4)
Disease Progression	3 (20)	3 (23)

Treatment Plan

This was a nonrandomized phase II trial with a primary endpoint of overall response by Response Evaluation Criteria in Solid Tumors and a secondary endpoint of TTP. Additional data on toxicity and overall survival (OS) were also captured as part of the protocol. Carboplatin dosages were based on the Calvert formula and used actual weight for calculating dose. After premedication with granisetron (Kytril®) 1 mg intravenous (I.V.) plus dexamethasone 10 mg I.V., patients received I.V. carboplatin at AUC = 2.0 (Calvert formula) over 1 hour followed by I.V. gemcitabine 800 mg/m^2 in 250 cc normal saline over 1 hour, both drugs administered weekly × 2 with a 1-week rest. Filgrastim starting on day 9 was administered at the discretion of the treating physician. Minimum treatment period for evaluability was 2 (3-week) cycles. Patients with complete response (CR), PR, or stable disease remained on study for ≥ 2 cycles. Patients having CR received 2 additional cycles of therapy (ie, CR + 2) and were then observed off therapy. To be considered evaluable for response, patients needed to receive ≥ 2 (3-week) cycles and live ≥ 4 weeks, while patients who received ≥ 1 cycle were evaluable for toxicity.

Table 2 Patient Characteristics

Patient No.	Age*	ER	PgR	HER2	Adjuvant Therapy	Previous Therapy	Sites of Disease
1	56	Neg	Neg	Neg	Cyclophosphamide/doxorubicin/5-FU	High-dose cyclophosphamide/doxorubicin/SCT	Lung, bone, pericardium
2	51	Pos	Pos	Pos	Docetaxel/trastuzumab	Vinorelbine	Lung, liver, bone
3	63	Neg	Neg	Pos	Cyclophosphamide/methotrexate/5-FU	Paclitaxel/trastuzumab	Liver, bone
4	56	Pos	Pos	Neg	Cyclophosphamide/methotrexate/5-FU/doxorubicin	Epirubicin/docetaxel	Liver
5	42	Pos	Neg	Neg	NA	Cyclophosphamide/doxorubicin	Chest wall, lung
6	43	Pos	Pos	Pos	NA	5-FU/doxorubicin/cyclophosphamide	NA
7	55	Neg	Neg	Neg	NA	Cyclophosphamide/doxorubicin/docetaxel	Lung, bone
8	42	Neg	Neg	Neg	NA	Cyclophosphamide/doxorubicin/docetaxel	Bone, mediastinum
9	55	Neg	Neg	Neg	Cyclophosphamide/doxorubicin	Docetaxel/capecitabine	Lung
10	55	Pos	Pos	Neg	NA	Paclitaxel	Liver, bone
11	54	Neg	Neg	Neg	NA	Docetaxel	Liver
12	44	Neg	Neg	Neg	Cyclophosphamide/doxorubicin	Docetaxel/capecitabine	Lung, bone, axilla
13	32	Neg	Neg	Neg	NA	Docetaxel	Chest wall, liver, lung
14	70	Pos	Pos	Pos	Cyclophosphamide/doxorubicin	Paclitaxel	Liver, lung
15	52	Neg	Neg	Neg	Cyclophosphamide/doxorubicin/docetaxel	Paclitaxel	Chest wall, bone

*Age is given in years.
Abbreviations: 5-FU = 5-fluorouracil; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NA = not available; Neg = negative; PgR = progesterone receptor; Pos = positive; SCT = stem cell transplantation

Table 3 Treatment-Related Toxicities

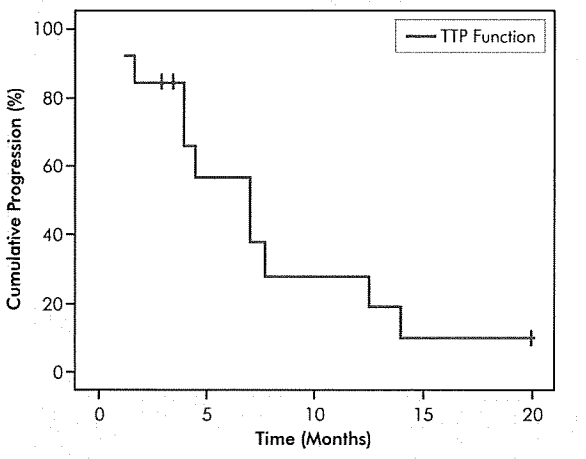
Toxicity	Patients (N = 15; %)
Anemia	
Grade 2	7 (46.6)
Grade 3	2 (13.3)
Grade 4	0
Neutropenia	
Grade 2	9 (60)
Grade 3	7 (46.6)
Grade 4	4 (26.6)
Thrombocytopenia	
Grade 2	7 (46.6)
Grade 3	4 (26.6)
Grade 4	3 (20)

Table 4 Dose Adjustments

Patient No.	Drug Adjusted	CSF Administered?
1	Gemcitabine	Yes
2	Gemcitabine	Yes
3	Gemcitabine	No
4	Gemcitabine	Yes
5	Gemcitabine	Yes
6	Gemcitabine	Yes
7	None	No
8	Gemcitabine	No
9	Gemcitabine	No
10	Gemcitabine	No
11	None	No
12	Gemcitabine	No
13	Gemcitabine	No
14	Gemcitabine and carboplatin	Yes
15	Gemcitabine	Yes

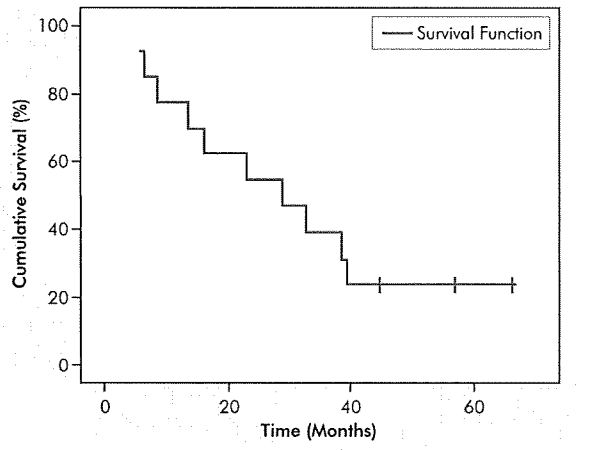
Abbreviation: CSF = colony-stimulating factor

Figure 1 Time to Progression



	Time to Progression	Standard Error	95% CI
Median	4.5 Months	1.26	(2.03-6.97)

Figure 2 Overall Survival



	Survival Time	Standard Error	95% CI
Median	28.8 Months	9.9	(9.4-48.2)

Results

Between January 2002 and December 2005, 15 patients were accrued to trial. Two patients developed clinical evidence of brain metastases during the first cycle of therapy and did not complete treatment. The remaining 13 patients were evaluable for response and toxicity. Table 1 provides the response data, Table 2 provides the patient characteristics, and Table 3 provides the toxicity results. There were no episodes of grade ≥ 2 alopecia, nausea and vomiting, skin rash, pulmonary toxicity, or neuropathy reported. Dose adjustments are provided in Table 4. Time to progression and OS are provided in Figures 1 and 2, respectively.

Discussion

Early detection and advances in treatment have improved the survival for early-stage node-negative breast cancer from 80% in the 1950s to 98% in 2007, yet the 5-year survival rate for patients with metastatic disease remains a disappointing 26%.[1] For patients at high risk and patients with metastatic disease, new treatment strategies are needed. Among the recent developments have been the application of dose-dense therapies, the introduction of targeted agents, and the more rational use of drug combinations.

Gemcitabine, a difluoro-substituted pyrimidine analogue, has been incorporated into a number of breast cancer therapies, including combination with paclitaxel, for which it received approval in relapsed disease.[16] The National Surgical Adjuvant Breast and Bowel Project B-38 study, due to complete accrual in 2008, includes a paclitaxel-plus-gemcitabine consolidation as 1 of the 3 arms of that trial.

Because platinum derivatives are among the most active drugs for the treatment of epithelial neoplasms, these agents have been increas-

ingly incorporated into breast cancer treatment. Despite early reports of low single-agent activity,[17] the platinum salts have revealed significant activity in breast cancer,[18] culminating in a trastuzumab-based regimen that has recently provided a 39% pathologic CR rate.[19]

Our and others' examination of gemcitabine/platinum combinations have been the subject of previous recently summarized report.[4] The repeating doublet schedules we have used in advanced breast and ovarian cancers were designed to maximize the synergy between these agents by exploiting the upregulation of NER associated with the exposure of tumor cells to platinum injury. The capacity to overcome platinum resistance in ovarian cancer[20] might also have relevance in breast cancer, a disease for which the related alkylating agents are widely used.

In our original series, the 50% response rate in heavily pretreated patients with breast cancer compared favorably with other regimens. Related regimens have provided response rates of 26%-52%[4-8] in relapsed and 54%-81%[10,11] in previously untreated patients with breast cancer. As carboplatin is used in gemcitabine-based therapies for non–small-cell lung and ovarian cancers, we developed this carboplatin-repeating doublet to capture the synergistic effects. The AUC of 2.0 for carboplatin was chosen to approximate the cisplatin 30 mg/m^2 dose used in our earlier studies.[13,21] We have previously shown that carboplatin and cisplatin reveal similar degrees of synergy with gemcitabine.[22] In addition, Nasr et al had reported a response rate of 33% in a phase II trial combining carboplatin AUC = 4.5 on day 1 with gemcitabine 1000 mg/m^2 days 1 and 8 every 21 days in patients relapsing after first-line therapy for metastatic disease.[14] More recently, a trial of carboplatin AUC = 4.0 on day 1 plus gemcitabine 1000 mg/m^2 days 1 and 8 provided a response rate of 31%.[15]

The current trial, with an intent-to-treat ORR of 53.3% and median TTP of 4.5 months (mean, 6.9 months; range, 1-20 months) compares favorably with our original report and with the results reported by Nasr[14] and Laessig.[15] The theoretical advantage for repeating doublet schedule to enhance synergy remains an interesting point with regard to the design of future clinical trials in this and other malignancies. Hematologic toxicities were manageable, but dose reductions in gemcitabine to 600 mg/m^2 (25%) were made in the majority of patients, with 7 of 15 (46.6%) requiring growth factor support. We had previously used gemcitabine 600 mg/m^2 as the starting dose for pretreated patients in our original cisplatin/gemcitabine trial.[13] The frequency of dose adjustments in this trial might suggest a greater degree of myelosuppression for carboplatin over cisplatin, but direct comparisons are difficult because of the different patient populations treated. There were no serious infections, bleeding episodes, or treatment-related deaths.

The original trial design used a Simon's 2-stage accrual, with the criterion for continuation being a response rate ≥ 30%. After the approval of gemcitabine in breast cancer, trial accrual slowed. This led to the decision to terminate further trial accrual. Nonetheless, the 61.5% ORR (95% CI, 32%-86%) in patients who received ≥ 1 cycle of therapy met the criterion of the 2-stage design for continuation. The observed activity and tolerable toxicity profile would support further evaluation of this carboplatin plus gemcitabine repeating doublet schedule.

Conclusion

The repeating doublet schedule of carboplatin plus gemcitabine in recurrent breast cancer reveals activity with tolerable toxicity. The objective response rate of 53.3%, by intent to treat, compares favorably with other platinum doublets in this disease. However, the frequency of dose reductions for gemcitabine and use of growth factor support in many patients would support the use of a starting dose of 600 mg/m^2 for gemcitabine in future studies. In combination with other cytotoxic agents, anti-vascular drugs or other targeted agents might offer additional opportunities for future studies of this and related platinum plus gemcitabine doublets in advanced breast cancer.

Acknowledgement

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9	55	Neg	Neg	Neg	Cyclophosphamide/doxorubicin	Docetaxel/capecitabine	Lung
10	55	Pos	Pos	Neg	NA	Paclitaxel	Liver, bone
11	54	Neg	Neg	Neg	NA	Docetaxel	Liver
12	44	Neg	Neg	Neg	Cyclophosphamide/doxorubicin	Docetaxel/capecitabine	Lung, bone, axilla
13	32	Neg	Neg	Neg	NA	Docetaxel	Chest wall, liver, lung
14	70	Pos	Pos	Pos	Cyclophosphamide/doxorubicin	Paclitaxel	Liver, lung
15	52	Neg	Neg	Neg	Cyclophosphamide/doxorubicin/docetaxel	Paclitaxel	Chest wall, bone

*Age is given in years.
Abbreviations: 5-FU = 5-fluorouracil; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NA = not available; Neg = negative; PgR = progesterone receptor; Pos = positive; SCT = stem cell transplantation

Table 3 Treatment-Related Toxicities

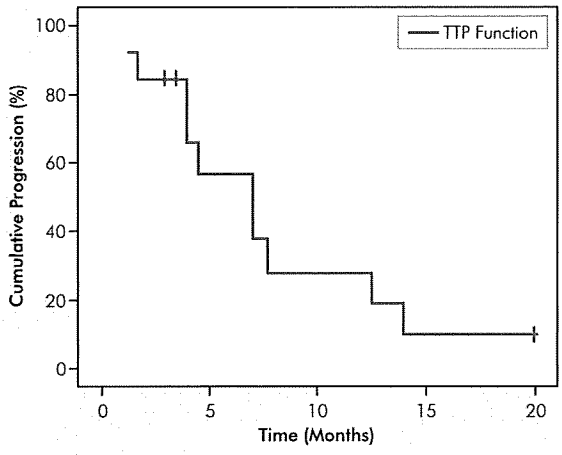
Toxicity	Patients (N = 15; %)
Anemia	
Grade 2	7 (46.6)
Grade 3	2 (13.3)
Grade 4	0
Neutropenia	
Grade 2	9 (60)
Grade 3	7 (46.6)
Grade 4	4 (26.6)
Thrombocytopenia	
Grade 2	7 (46.6)
Grade 3	4 (26.6)
Grade 4	3 (20)

Table 4 Dose Adjustments

Patient No.	Drug Adjusted	CSF Administered?
1	Gemcitabine	Yes
2	Gemcitabine	Yes
3	Gemcitabine	No
4	Gemcitabine	Yes
5	Gemcitabine	Yes
6	Gemcitabine	Yes
7	None	No
8	Gemcitabine	No
9	Gemcitabine	No
10	Gemcitabine	No
11	None	No
12	Gemcitabine	No
13	Gemcitabine	No
14	Gemcitabine and carboplatin	Yes
15	Gemcitabine	Yes

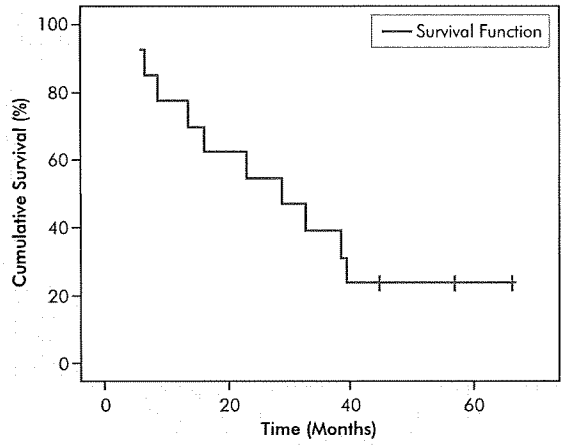
Abbreviation: CSF = colony-stimulating factor

Figure 1 Time to Progression



	Time to Progression	Standard Error	95% CI
Median	4.5 Months	1.26	(2.03-6.97)

Figure 2 Overall Survival



	Survival Time	Standard Error	95% CI
Median	28.8 Months	9.9	(9.4-48.2)

Results

Between January 2002 and December 2005, 15 patients were accrued to trial. Two patients developed clinical evidence of brain metastases during the first cycle of therapy and did not complete treatment. The remaining 13 patients were evaluable for response and toxicity. Table 1 provides the response data, Table 2 provides the patient characteristics, and Table 3 provides the toxicity results. There were no episodes of grade ≥ 2 alopecia, nausea and vomiting, skin rash, pulmonary toxicity, or neuropathy reported. Dose adjustments are provided in Table 4. Time to progression and OS are provided in Figures 1 and 2, respectively.

Discussion

Early detection and advances in treatment have improved the survival for early-stage node-negative breast cancer from 80% in the 1950s to 98% in 2007, yet the 5-year survival rate for patients with metastatic disease remains a disappointing 26%.[1] For patients at high risk and patients with metastatic disease, new treatment strategies are needed. Among the recent developments have been the application of dose-dense therapies, the introduction of targeted agents, and the more rational use of drug combinations.

Gemcitabine, a difluoro-substituted pyrimidine analogue, has been incorporated into a number of breast cancer therapies, including combination with paclitaxel, for which it received approval in relapsed disease.[16] The National Surgical Adjuvant Breast and Bowel Project B-38 study, due to complete accrual in 2008, includes a paclitaxel-plus-gemcitabine consolidation as 1 of the 3 arms of that trial.

Because platinum derivatives are among the most active drugs for the treatment of epithelial neoplasms, these agents have been increas-

ingly incorporated into breast cancer treatment. Despite early reports of low single-agent activity,[17] the platinum salts have revealed significant activity in breast cancer,[18] culminating in a trastuzumab-based regimen that has recently provided a 39% pathologic CR rate.[19]

Our and others' examination of gemcitabine/platinum combinations have been the subject of previous recently summarized report.[4] The repeating doublet schedules we have used in advanced breast and ovarian cancers were designed to maximize the synergy between these agents by exploiting the upregulation of NER associated with the exposure of tumor cells to platinum injury. The capacity to overcome platinum resistance in ovarian cancer[20] might also have relevance in breast cancer, a disease for which the related alkylating agents are widely used.

In our original series, the 50% response rate in heavily pretreated patients with breast cancer compared favorably with other regimens. Related regimens have provided response rates of 26%-52%[4-8] in relapsed and 54%-81%[10,11] in previously untreated patients with breast cancer. As carboplatin is used in gemcitabine-based therapies for non–small-cell lung and ovarian cancers, we developed this carboplatin-repeating doublet to capture the synergistic effects. The AUC of 2.0 for carboplatin was chosen to approximate the cisplatin 30 mg/m^2 dose used in our earlier studies.[13,21] We have previously shown that carboplatin and cisplatin reveal similar degrees of synergy with gemcitabine.[22] In addition, Nasr et al had reported a response rate of 33% in a phase II trial combining carboplatin AUC = 4.5 on day 1 with gemcitabine 1000 mg/m^2 days 1 and 8 every 21 days in patients relapsing after first-line therapy for metastatic disease.[14] More recently, a trial of carboplatin AUC = 4.0 on day 1 plus gemcitabine 1000 mg/m^2 days 1 and 8 provided a response rate of 31%.[15]

The current trial, with an intent-to-treat ORR of 53.3% and median TTP of 4.5 months (mean, 6.9 months; range, 1-20 months) compares favorably with our original report and with the results reported by Nasr[14] and Laessig.[15] The theoretical advantage for repeating doublet schedule to enhance synergy remains an interesting point with regard to the design of future clinical trials in this and other malignancies. Hematologic toxicities were manageable, but dose reductions in gemcitabine to 600 mg/m^2 (25%) were made in the majority of patients, with 7 of 15 (46.6%) requiring growth factor support. We had previously used gemcitabine 600 mg/m^2 as the starting dose for pretreated patients in our original cisplatin/gemcitabine trial.[13] The frequency of dose adjustments in this trial might suggest a greater degree of myelosuppression for carboplatin over cisplatin, but direct comparisons are difficult because of the different patient populations treated. There were no serious infections, bleeding episodes, or treatment-related deaths.

The original trial design used a Simon's 2-stage accrual, with the criterion for continuation being a response rate ≥ 30%. After the approval of gemcitabine in breast cancer, trial accrual slowed. This led to the decision to terminate further trial accrual. Nonetheless, the 61.5% ORR (95% CI, 32%-86%) in patients who received ≥ 1 cycle of therapy met the criterion of the 2-stage design for continuation. The observed activity and tolerable toxicity profile would support further evaluation of this carboplatin plus gemcitabine repeating doublet schedule.

Conclusion

The repeating doublet schedule of carboplatin plus gemcitabine in recurrent breast cancer reveals activity with tolerable toxicity. The objective response rate of 53.3%, by intent to treat, compares favorably with other platinum doublets in this disease. However, the frequency of dose reductions for gemcitabine and use of growth factor support in many patients would support the use of a starting dose of 600 mg/m^2 for gemcitabine in future studies. In combination with other cytotoxic agents, anti-vascular drugs or other targeted agents might offer additional opportunities for future studies of this and related platinum plus gemcitabine doublets in advanced breast cancer.

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