Investigational New Drugs **11**: 75-79, 1993.

Phase II trial of doxorubicin and trifluoperazine in metastatic breast cancer

G.T. Budd, R.M. Bukowski, A. Lichtin, L. Bauer, P. Van Kirk and R. Ganapathi
Department of Hematology/Medical Oncology, Desk T-33, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Key words: doxorubicin, trifluoperazine, breast cancer, drug resistance

Summary

Pre-clinical and clinical studies have shown that trifluoperazine (TFP) can modulate multidrug resistance. We have performed a Phase II trial of TFP and doxorubicin in doxorubicin-naive patients with metastatic breast cancer. We hypothesized that TFP would inhibit the development of doxorubicin resistance, resulting in an increased rate of complete response or a prolongation in response duration. Twenty patients with metastatic breast cancer were treated every 3 weeks with TFP 5 mg by mouth every 6 hours on days 0–5 and doxorubicin 60 mg/m^2/96 hr on days 1–4 by continuous intravenous infusion. The first 5 patients were treated with TFP 15 mg by mouth every 6 hours, but the dose was reduced to 5 mg every 6 hours when grade 3–4 extrapyramidal toxicity was noted in 3 of the first 5 patients. Thereafter, neurologic toxicity was grade 0–2. No complete and 9 partial responses were produced in 20 patients (45%). The median response duration was 17 weeks (range 7–112). The combination of trifluoperazine and doxorubicin did not seem to produce a response rate or duration markedly different than that expected for doxorubicin alone in patients with metastatic breast cancer. Alternative trial designs may be necessary in future clinical trials investigating the inhibition of acquisition of drug resistance.

Introduction

The systemic therapy of metastatic breast cancer is currently palliative, with only a very few patients entering long-term complete remission. The acquisition of drug resistance by metastatic breast cancer cells is a major problem, as demonstrated by the fact that, while most patients initially respond to chemotherapy, disease progression is inevitable despite continued treatment. A laboratory correlate of the clinical observation that patients whose disease is refractory to one type of chemotherapy tend to be resistant to other types of chemotherapy has been found with the identification of multidrug resistance in tumor model systems [1]. Studies of the mechanism underlying multidrug resistance have identified a number of changes in resistant tumors. These include the expression of the drug transport protein P-170 [2,3], altered topoisomerase II activity [4], and alterations in glutathione metabolism [5].

With the identification of mechanisms of resistance have come attempts to pharmacologically modulate these mechanisms. A number of agents, including verapamil and reserpine, have been reported to reverse multidrug resistance *in vitro* [6,7]. Calmodulin inhibitors, such as trifluoperazine, were among the first agents reported to enhance the accumulation, retention, and cytotoxicity of doxorubicin and vincristine in drug-resistant cell lines [7–9]. Based upon these preclinical studies, clinical trials have been performed in patients with drug resistant tumors. An early trial, using high dose verapamil and doxorubicin in resistant ovarian cancer, failed to produce responses in refractory ovarian cancer, perhaps be-

cause toxicity prevented adequate escalation of the dose of verapamil [9]. Another trial used verapamil with the combination of vincristine, doxorubicin, and dexamethasone to treat refractory B-cell malignancies. In this study, objective responses were observed, with all of the responses being produced in those patients whose tumors expressed the P-glycoprotein [10]. We studied the combination of trifluoperazine and doxorubicin in patients whose tumors had progressed during doxorubicin-containing chemotherapy [11]. In that trial, objective responses were observed, but only in those patients whose tumors had initially responded to doxorubicin-based chemotherapy and subsequently progressed. The dose of trifluoperazine was escalated in a phase I trial design. Responses were seen at the lowest dose of trifluoperazine studied (20 mg/day); the maximum tolerated dose was 60 mg/day.

Based upon this trial of trifluoperazine and doxorubicin, we undertook the current trial. Patients with metastatic breast cancer and no prior anthracycline exposure were treated with the combination of doxorubicin and trifluoperazine, based upon the hypothesis that co-treatment with trifluoperazine would inhibit the acquisition of doxorubicin resistance and result in an improved response quality (complete response rate) and a prolongation of response duration.

Materials and methods

This trial was open to patients with metastatic or recurrent breast cancer with measurable disease. Patients were required to be either estrogen-receptor negative or to have failed hormonal therapy. Patients were required to be of SWOG Performance Status 0–2 and to have received 0–1 prior chemotherapy regimens for metastatic or recurrent disease. Adequate bonemarrow, hepatic, and renal function were required. Patients were excluded from entry if they had received anthracyclines previously or if they had congestive heart failure or a history of significant cardiac disease. Patients were required to have recovered from their previous therapy and to give their informed consent to participation.

Patients were treated with doxorubicin at a dose of 60 mg/m^2, administered as a continuous intravenous infusion over 96 hours on days 1–4 of each 3 week treatment cycle. Trifluoperazine was given at a dose of 15 mg by mouth every 6 hours (60 mg/day) on days 0–6 of each three week treatment cycle; that is, trifluoperazine was begun 24 hours before each doxorubicin infusion and continued until 24 hours after the completion of each doxorubicin infusion. Because grade 3–4 neurologic toxicity was noted in 3 of the first 5 patients treated with trifluoperazine at a dose of 15 mg every 6 hours, and because objective responses to the combination of trifluoperazine and doxorubicin had been observed with a dose of trifluoperazine of 5 mg in our phase I study, the dose of trifluoperazine was reduced to 5 mg by mouth every 6 hours for all subsequent patients entered on trial.

Patients were seen and examined every 3 weeks, at which time serum chemistry profiles and a complete blood count were performed. Disease which could be measured by chest X-ray or physical examination was assessed every 3 weeks; disease that was measurable by special radiographic studies (e.g., computed tomagraphy) was assessed every 6 weeks. Toxicity was graded according the National Cancer Institute Common Toxicity Criteria. Conventional response definitions were used. That is, a 50% or greater decrease in the sum of the products of the longest diameters and the longest perpendicular diameters of prospectively identified measurable lesions was required for a response to be termed a partial response, and complete disappearance of all known disease was required for a response to be termed complete. All responses were required to persist for 4 or more weeks. The time to treatment failure was defined as the time between entry on study and removal from the study for any reason (progression, toxicity, or death). Response duration was defined as the time between achieving a partial response and removal from the study. Survival was measured from the time of entry on study and death or last follow-up.

Table 1. Patient characteristics

Entered	20
Eligible	20
Evaluable	20
Age median	51 yrs
range	23–68
Pre-meno	12
Post-meno	8
Prior chemo	15
Adjuvant only	5
For metastases only	8
Both	2
Prior radiotherapy	14

Table 2. Tumor characteristics

Nodal status at diagnosis	
Node −	8
Node +	11
Stage IV	1
Hormone receptor status	
ER +	5
ER −	15
PR +	3
PR −	17
Sites of involvement	
Lung	15
Local/Regional	13
Bone	12
Liver	12
Brain	1
Number of involved sites	
Median	2.5
Range	1–5

Results

Patient and tumor characteristics are summarized in Tables 1 and 2. Toxicity is summarized in Table 3. Among the 5 patients treated with trifluoperazine 15 mg every 6 hours, 3 cases of Grade 3–4 neurotoxicity were observed, consisting of tardive dyskinesia or extrapyramidal effects poorly controlled by therapy. Patients treated with trifluoperazine at a dose of 5 mg every 6 hours had grade 0–2 neurotoxicity, consisting primarily of sedation or mild extrapyramidal effects. Myelosuppression and mucositis were observed at a severity typical for doxorubicin 60 mg/m^2 administered as a 96 hour continuous infusion.

Table 3. Maximum toxicity grade per patient (Total # patients = 20)

Toxicity description	Grade	# Patients
Extrapyramidal syndrome		
Minor, controlled	1–2	16
Poorly controlled	3	2
Tardive dyskinesia	4	1
Mucositis		
Mild ulcers	1–2	7
Liquid diet needed	3	1
Intravenous fluids	4	0
Leukopenia ($\times 10^9$/L)		
2.0–3.9	1–2	5
1.0–1.9	3	11
< 1.0	4	2
Granulocytopenia		
1.0–1.9	1–2	5
0.5–0.9	3	8
< 0.5	4	4
Thrombopenia		
50–99	1–2	1
25–49	3	1
< 25	4	0

No complete and 9 partial responses were observed in the 20 patients entered, resulting in an objective response rate of 45%. The median time to treatment failure was 12 weeks (range, 6–126 weeks); the median time to treatment failure of responders was 28 weeks (range 10–126 weeks); the median response duration was 17 weeks (range 7–112 weeks); the median survival of all patients entered on trial, dating from entry on study, was 45 weeks (range 6–191$^+$).

Discussion

Table 4 compares the results of this study with several recent reports of treatment with single agent doxorubicin in metastatic breast cancer. The overall objective response rate, complete response rate, and duration of treatment effect produced by therapy with trifluoperazine and doxorubicin is not greatly different than that produced by treatment with doxorubicin alone. We were unable to demon-

Table 4. Single-agent doxorubicin in breast cancer

Ref.	Dose doxorubicin	Number patients	% CR + PR	Median time to treatment failure	Median survial
12	75 mg/m^2	42	47%	21 weeks	37 weeks
13	60 mg/m^2	40	30%	19 weeks	not given
14	75 mg/m^2	140	29%	15 weeks	38 weeks
15	60 mg/m^2	130	28%	19 weeks	45 weeks
Current study	60 mg/m^2	20	45%	12 weeks	45 weeks

strate an effect of trifluoperazine on the development of clinical doxorubicin resistance. It is possible that the amended dose of trifluoperazine of 5 mg every 6 hours was too low to produce the desired effects. In our phase I trial, plasma levels of trifluoperazine were much lower than the concentrations of trifluoperazine used *in vitro*, regardless of dose. However, because the volume of distribution of trifluoperazine is large, it is likely that plasma levels do not accurately reflect tissue levels of the drug. Furthermore, objective responses to doxorubicin with trifluoperazine 5 mg every 6 hours were observed in our phase I trial, implying that this dose can produce tissue concentrations of trifluoperazine sufficient to modulate doxorubicin resistance.

Another possibility is that any modulation of the acquisition of resistance to doxorubicin was obscured by the inclusion in the trial of tumors that were intrinsically resistant to doxorubicin. In our phase I study, no objective responses were seen in patients whose tumors were intrinsically resistant to doxorubicin. Because the objective response rate to single agent doxorubicin in breast cancer is less than 50%, a minority of cases of breast cancer are intrinsically sensitive to doxorubicin. It is only in these tumors that trifluoperazine would be expected to produce a delay in the development of resistance. It is possible that responses were prolonged by trifluoperazine, but that the number of patients benefitting from trifluoperazine was insufficient to affect the median response duration.

An alternative trial design, in which patients responding to single agent doxorubicin would be randomly assigned to receive continued doxorubicin alone or the combination of doxorubicin and trifluoperazine, might allow the role of trifluoperazine to be better examined, but would necessitate that a large number of patients be entered on trial. Another approach would be to serially monitor patients receiving doxorubicin, seeking to characterize the mechanisms underlying drug resistance in individual patients' tumors. Thus, while the current study did not demonstrate that a delay in the development of resistance to doxorubicin was produced by trifluoperazine treatment, investigation of drug resistance and its modulation should continue. Such investigations may require novel trial designs and correlative laboratory studies.

References

1. Kessel D, Botteril V, Wodinski I: Uptake and retention of daunomycin by mouse leukemic cells as factors in drug response. Cancer Research 28:938–941, 1968
2. Shen DW, Fojo A, Chin JE, Roninson IB, Richert N, Pastan I, Gottesman MM: Human multidrug-resistant cell lines: increased mdrl expression can precede gene amplification. Science 232:643–645, 1986
3. Shen DW, Fojo A, Roninson IB, Chen JE, Soffir R, Pastan I, Gottesman MM: Multidrug resistance of DNA-mediated transformants is linked to transfer of the human mdrl gene. Molecular and Cellular Biology 6:4039–4045, 1986
4. Pommier Y, Kerrigan D, Schwartz RE, Swack JA, McCurdy A: Altered DNA topoisomerase II activity in Chinese Hamster cells resistant to topoisomerase II inhibitors. Cancer Research 46:3075–3081, 1986
5. Tsuruo T, Iida H, Tsukagoshi S, Sakurai Y: Overcoming of vincristine resistance in P388 leukemia in vivo and in vitro through enhanced by cytotoxicity of vincristine and vinblastine by verapamil. Cancer Research 41:1967–1972, 1981
6. Inaba M, Fujikura R, Tsukagoshi S, Sakurai Y: Restored in vitro sensitivity of adriamycin- and vincristine-resistant P388 leukemia with reserpine. Biochemical Pharmacology 30:2191–2194, 1981
7. Ganapathi R, Grabowski D: Enhancement of sensitivity to Adriamycin in resistant P388 leukemia by the calmodulin inhibitor trifluoperazine. Cancer Research 43:3696–3699, 1983

8. Tsuruo T, Iida H, Tsukagoski S, Sakurai Y: Increased accumulation of vincristine and Adriamycin in drug-resistant P388 tumor cells following incubation with calcium antagonists and calmodulin inhibitors. Cancer Research 42:4730–4733, 1982
9. Ozols RF, Cunnionb RE, Klecker RW, Hamilton TC, Ostechaga Y, Parrillo JE, Young RC: Verapamil and Adriamycin in the treatment of drug-resistant ovarian cancer patients. Journal of Clinical Oncology 5:641–647, 1987
10. Dalton WS, Grogan TM, Moltzer PS, Scheper RJ, Durie BCM, Taylor CW, Miller TP, Salmon SE: Drug-resistance in multiple myeloma and non-Hodgkin's lymphoma: detection of P-glycoprotein and potential circumvention by addition of verapamil to chemotherapy. Journal of Clinical Oncology 7:415–424, 1989
11. Miller RL, Bukowski RM, Budd GT, Purvis J, Weick JK, Shepard K, Midha KK, Ganapathi R: Clinical modulation of doxorubicin resistance by the calmodulin-inhibitor, trifluoperazine: a Phase I/II trial. Journal of Clinical Oncology 6:880–888, 1988
12. Andersson M, Daugaard S, von der Maase, Mouridsen HT: Doxorubicin versus mitomycin versus doxorubicin plus mitomycin in advanced breast cancer: a randomized study. Cancer Treatment Reports 70:1181–1186, 1986
13. Neidhart JA, Gochnour D, Roach R, Hoth D, Young D: A comparison of mitoxantrone and doxorubicin in breast cancer. Journal of Clinical Oncology 4:672–677, 1986
14. Henderson IC, Allegra JC, Woodcock T, Wolff S, Bryan S, Cartwright K, Dukart G, Henry D: Randomized clinical trial comparing mitoxantrone with doxorubicin in previously treated patients with metastatic breast cancer. Journal of Clinical Oncology 7:560–571, 1989
15. Cowan JD, Neidhart J, McClure S, Coltman CA, Gumbart C, Martino S, Hutchins LF, Stephens RL, Vaughan CB, Osborne CK: Randomized trial of doxorubicin, bisantrene, and mitoxantrone in advanced breast cancer: a Southwest Oncology Group study. Journal of Clinical Oncology 83:1077–1084, 1991

Address for offprints: G.T. Budd, Department of Hematology/Medical Oncology, Desk T-33, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA