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Phase I trial of combined therapy with bleomycin and the calmodulin antagonist, trifluoperazine*,**

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Summary. Calmodulin antagonists, such as trifluoperazine, can enhance the cytotoxic effects of bleomycin both in tissue culture and in vivo. Therefore, we evaluated the effects of combination treatment with these drugs in a phase I clinical trial. Patients with objectively measurable or evaluable cancer refractory to conventional treatment who had an acceptable performance status (ECOG 0-2) and acceptable laboratory studies were eligible. All patients gave written informed consent. A cycle of therapy consisted of three weekly treatments with trifluoperazine (days 1–4) and 30 IU bleomycin (day 3). After three patients completed a cycle of therapy without experiencing dose-limiting toxicity, new patients were entered in the study and received a higher dose of trifluoperazine. The dose of bleomycin remained constant. Evaluable patients received at least 2 weeks of treatment and survived for 6 weeks; of 19 patients, 2 were unevaluable. The major toxicities were neurological and pulmonary and included one case of fatal pneumonia with interstitial pulmonary fibrosis. There was no hematologic toxicity. Two patients underwent partial responses (PRs) and two had complete responses (CRs). We conclude that trifluoperazine can safely be given with bleomycin and that further study of the potential efficacy of this treatment is indicated.

Introduction

The cytotoxic effects of bleomycin are markedly enhanced in certain malignant cell lines by a group of drugs that share the property of antagonizing the action of calmodulin (CaM) [13, 18, 19]. CaM is a ubiquitous calcium-binding protein that regulates several important aspects of cellular metabolism, including cyclic nucleotide synthesis and degradation [5], protein phosphorylation [27] and dephosphorylation [30], ATP homeostasis [9, 15], glycogen metabolism [6], and the formation of the microtubular apparatus [23]. These and other functions strongly suggest an essential role for CaM in eukaryotic cellular proliferation [2, 16, 24]. The discovery by Levin and Weiss [21] that phenothiazines and structurally related compounds can antagonize the action of this molecule led us [11, 12, 20] and others [14, 29] to study their antineoplastic effects. We have shown that this group of drugs possessed broad-spectrum cytotoxic activity [11, 12] and that this toxicity was correlated with their potency as CaM antagonists [12, 20]. We further observed that CaM antagonists markedly augment the lethal effects of bleomycin [13, 18] and that this augmentation is most marked in tumor cells that are naturally resistant to bleomycin [19]. The observation that CaM antagonists increased the DNA damage caused by bleomycin led to the proposal that the mechanism of enhancement was due to inhibition by phenothiazines of a CaM-sensitive process of DNA repair [4, 17]. The rationale for using CaM antagonists in the clinical treatment of malignant diseases has recently been reviewed [10]. We report the results of a phase I study testing the effects of a combination of the CaM antagonist trifluoperazine and the glycopeptide antibiotic bleomycin.

Methods

Nonpregnant, nonlactating patients between the ages of 18 and 76 with objectively measurable or evaluable, histologically confirmed cancer refractory to conventional forms of therapy were eligible for entry. Patients were required to have an expected survival of over 6 weeks and an ECOG performance status of <3.

Laboratory parameters required for eligibility included: a pulmonary diffusing capacity of $>50\%$ of the predicted value; serum creatinine levels of <2.0 mg/dl or creatinine clearance of >35 ml/min; a WBC count of $>3{,}500/mm^3$ with an absolute granulocyte count of $>1{,}500/mm^3$; hemoglobin values of >10 gm/dl; a platelet count of $>100{,}000/mm^3$; serum calcium levels of <12 mg/dl; total bilirubin levels of <2.5 mg/dl; serum glutamic oxaloacetic transaminase (SGOT) and/or serum glutamic pyruvate transminase values <2 times the upper limit of normal; and alkaline phosphatase and/or 5'-nucleotidase levels <2 times the upper limit of normal.

Criteria for ineligibility into this study included: other therapy (chemotherapy or radiation) during the 4 weeks prior to entry or treatment with a nitrosourea or mitomycin C in the 6 weeks prior to entry; prior radiation to the mediastinum or lungs; current treatment with antipsychotics, seda-

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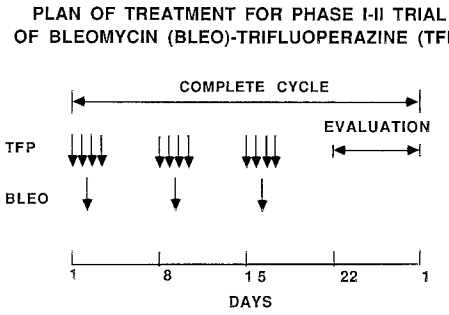

Fig. 1. Plan of treatment for phase I–II trial of bleomycin (BLEO)-trifluoperazine (TFP). All patients received TFP on days 1–4 of each week and on day 3 of each week for 3 consecutive weeks. During the 4th week a complete reevaluation was carried out as described in *Methods*

tive hypnotics, or antidepressants; prior treatment with bleomycin; documented adverse reactions to trifluoperazine; significant organic heart disease (congestive heart failure, unstable angina pectoris, high-grade arrythmias), asthma or chronic obstructive pulmonary disease requiring therapy with bronchodilators; nonmalignant interstitial pulmonary disease; or major psychiatric disability. Prior to entry, written informed consent was obtained from each patient in accordance with the guidelines of the Yale University School of Medicine's Human Investigation Committee.

Design of study. The plan of treatment is shown in Fig. 1. All patients received therapy weekly for 3 weeks followed by a 1-week period of rest during which a complete reevaluation was carried out; this 4-week period constituted one evaluable cycle. Patients received trifluoperazine (Stelazine, Smith-Kline and Beckman) orally twice daily for 4 days of each week. At treatment level I, patients received a dose of 3 mg trifluoperazine b.i.d.; at subsequent levels, the dose was escalated to 6 mg (level II), 9 mg (level III), and 12 mg b.i.d. (level IV). Bleomycin (Blenoxane, Bristol Laboratories) was given on the 3rd day of treatment with trifluoperazine each week at a dose of 30 IU i.v. infused over 30 min. No antiemetics were given. Acetaminophen was taken as needed for chills and fever, which usually occurred during the first 24 h after the dose of bleomycin.

A minimum of three patients were required to complete a dose level without developing grade 3 toxicity (see below) before patients could be entered into the study at a higher dose of trifluoperazine. If dose-limiting toxicity (see below) occurred in two of three patients at a given level, three new patients were required to enter and complete the same level. After completing one cycle, patients could continue receiving treatment at the same dose level as long as (1) they did not experience dose-limiting toxicity; (2) their disease had not progressed; and (3) they had received less than a total of 300 IU bleomycin. Once entered into the study, patients could not move up to a higher dose level. Patients were evaluable if they had completed at least 2 weeks of treatment or if, regardless of the number of treatments, they could not receive any further therapy due to toxicity.

Prior to the initiation of treatment and during the 4th week of each cycle, all patients underwent an evaluation consisting of a complete history and physical examination, an assessment of performance status, laboratory tests that included a complete blood count, serum electrolytes, blood urea nitrogen (BUN), creatinine, liver function tests, calcium, phosphate, chest X-ray, electrocardiogram, and pulmonary function tests (lung volumes, flow rates, flow-volume loop, and diffusing capacity). Pulmonary function tests were repeated monthly for an additional 3 months after the completion of therapy.

Evaluation of toxicity. All patients were evaluated weekly for evidence of toxicity, which was assessed and graded using the WHO criteria. Dose-limiting toxicity was defined as the occurrence of side effects severe enough to prohibit the further use of additional drug. The presence of a worsening cough, dyspnea, new rales, or a 10% decrease in pulmonary diffusion capacity led to the immediate discontinuation of treatment. Dose-limiting toxicities for other organ systems were defined as $\geq$ grade 3 toxicity.

Evaluation of response. This study was designed to include the evaluation of responses by direct measurement of tumors or evaluation of diagnostic radiologic tests. Responses were defined as follows:

Complete response (CR): The disappearance of all known disease, determined by two measurements not less than 4 weeks apart, without the appearance of new lesions.

Partial response (PR): A $\geq$ 50% decrease in total tumor size, determined by the sum of the greatest perpendicular diameters of all measurable lesions documented by two observations not less than 4 weeks apart, in the absence of the appearance of new lesions.

Stable disease (S): A 50% decrease in total tumor size could not be established, nor did a 25% increase in the size of one or more measurable lesions occur, and there was no appearance of new lesions.

Progressive disease (PD): A $\geq$ 25% increase in the size of one or more measurable lesions and/or the appearance of new lesions.

Quality control. All patients were entered into this study through the Clinical Research Office of the Yale University Comprehensive Cancer Center. At the time of entry, the eligibility criteria were reviewed and checked by an oncology nurse specialist/data manager (K. W.), who subsequently maintained a central flow chart on each patient and ensured that follow-up tests were scheduled, completed, and accurately recorded. Each patient enrolled in the study was seen weekly by the data manager and one of the investigators. The evaluation of toxicity and response was determined by at least two of the investigators by a review of the physical examination and diagnostic studies.

Results

A total of 19 patients were enrolled in the study and all but 2 were evaluable; the characteristics of these patients are shown in Table 1. The mean age was 55 years, with a range of 27–76 years. The mean performance status was 0.5; all individual values are listed in Table 1. All patients had received previous chemotherapy with no more than two regimens, and 13 had received prior radiation therapy. None of the patients had received prior radiation to the chest or prior treatment with potential pulmonary toxins.

Two patients were unevaluable: one died of progressive disease (Paget's sarcoma with extensive pulmo-

Table 1. Summary of results of a phase I trial of bleomycin-trifluoperazine

Patient	Age	Sex	PS	Diagnosis	Treatment level	Toxicity		Response	
						1st	Additional	1st	Additional
1	53	F	1	Breast	I[a]	2 CNS	–	P	–
2	58	F	0	Cervix	I[d]	2 CNS	3 CNS/1 Pulm	S	S
3	63	M	1	Bladder	I[b]	1 Chills	1 CNS	P	–
4	65	F	0	Ovary	I[c]	1 CNS	3 CNS	S	S
5	51	M	2	H/N	I[a]	0	–	P	–
6	73	M	1	H/N	II[a]	2 Cardiac	–	UE	–
7	62	M	0	Pagets	II[a]	0	–	P	–
8	35	F	0	MF	II[b]	2 CNS	2 CNS	PR	PR
9	76	F	0	Ovary	II[d]	2 CNS	2 CNS	S	S
10	56	F	0	MF	II[c]	1 Chills	3 CNS	PR	–
11	65	F	0	Renal	III[a]	1 CNS	–	P	–
12	27	F	0	MF	III[b]	3 CNS	3 CNS	S	P
13	22	F	0	Renal	III[a]	3 CNS	–	S	–
14	62	M	0	MF	III[c]	1 CNS	5 Pulm	PR	CR
15	58	M	0	MF/CUP	III[b]	2 CNS	1 Pulm	S	CR
16	51	M	1	NSCLC	III[a]	4 SZS	–	S	–
17	60	F	2	Ovary	III[a]	2 CNS	–	S	–
18	66	F	1	Endometrium	III[a]	3 CNS	–	P	–
19	41	M	2	H/N	III[a]	3 CNS	–	UE	–

Abbreviations: PS, performance status; F, female; M, male; H/N, squamous cell carcinoma of the head and neck; Pagets, Pagets sarcoma; MF, mycosis fungoides; CUP, carcinoma of unknown primary; NSCLC, non-small-cell lung cancer; P, endometrial carcinoma (endometrium) progression; PR, partial response; CR, complete response; S, stable disease; CNS, central nervous system; PULM, pulmonary; SZS, seizures; UE, unevaluable

[a] 1 cycle
[b] 2 cycles
[c] 3 cycles
[d] 4 cycles

nary metastases and pleural effusion) 1 week after the start of therapy. The other patient inadvertently took a single 12-mg dose of trifluoperazine and experienced transient hypotension; he chose not to receive further treatment.

The major forms of toxicity were neuropsychiatric and pulmonary. No measurable hematopoietic toxicity occurred. Overall, the neuropsychiatric toxicity was tolerable, most symptoms consisting of mild sedation or mild akathisia (seven patients). Other neuropsychiatric toxicities included alteration in mood, somnolence, anxiety, hyperactivity, and depression. The severity of these symptoms were related to the dose and duration of therapy with trifluoperazine. For example, after one cycle, grade 2 toxicity was observed in only one of five patients at level I but in two of four at level II. Grade 3 toxicity, including depersonalization and emotional lability and/or depression, was observed in two of three patients at level III; an additional five patients were entered at this level, and four experienced grade 3 toxicity. Therefore, the side effects of 9 mg b.i.d. (level III) were severe enough to justify this as the maximum tolerated dose. The onset of symptoms was usually seen by the third day of treatment, resolving within 72 h of stopping the phenothiazine.

All neuropsychiatric side effects were completely reversible on discontinuation of the drug. After one cycle of treatment, one patient with known pulmonary spread of carcinoma of the breast experienced worsening pulmonary function that could be attributed to the progressive lymphatic spread of carcinoma of the breast, although bleomycin toxicity could not be unequivocally excluded. No other patients showed evidence of pulmonary toxicity after either one cycle of treatment or 3 months of follow-up.

Chemotherapy was continued beyond one cycle in nine patients, four of whom experienced grade 3 neurologic toxicity (two patients at level I, one at level II, and one at level III) consisting of severe depression. Pulmonary toxicity was seen in three of these nine patients. Two patients experienced grade 1 pulmonary toxicity after receiving 300–320 IU bleomycin. Following the discontinuation of treatment, no further pulmonary dysfunction was detected over a minimum of 3 months of follow-up. A third patient suffered fatal pulmonary toxicity after receiving 270 IU (see below). Minor toxicities included a pruritic erythematous rash in one patient that resolved with diphenhydramine and, after receiving bleomycin, several patients experienced rigors that resolved with acetaminophen. All toxicity, except in the patient with fatal pulmonary damage, was reversible upon discontinuation of the treatment.

The effect of a single vs multiple cycles of treatment on measurable disease are shown in Table 1. After one cycle, a regression (PR) of the tumor was noted in three patients. Two patients (14 and 15) underwent CRs after three cycles of treatment at level III. Patient 14 had tumor and plaque-stage mycosis fungoides involving >80% of his body surface area (stage III). He had previously been treated with total-body electron-beam radiation (3600 rads, 6 MeV) followed by 6 monthly cycles of doxorubicin, 30 mg/m^2 on day 1, and cyclophosphamide, 100 mg/m^2 p.o. on days 1–14 [3]. This patient relapsed within 3 months after completing this regimen and was started on ProMACE-MOPP [7]; his disease progressed during the second cycle. He then entered the current study at level III and received a combination of 9 mg trifluoperazine b.i.d. with 30 IU bleomycin weekly. After two cycles he entered a complete clinical

remission; after the third cycle, his pulmonary diffusing capacity had decreased by 10% and further therapy was withheld. Despite treatment with high doses of steroids, the patient developed worsening pulmonary function, right ventricular congestive heart failure, and bacterial pneumonia and died of progressive respiratory failure. A postmortem examination revealed marked interstitial pulmonary fibrosis and bronchopneumonia. There was no evidence of residual lymphoma.

Patient 15 had two malignancies, plaque-stage mycosis fungoides involving 25% of his body surface, and multiple metastatic lesions in the lung that biopsy revealed to be adenocarcinoma. The primary tumor was unknown. Both lesions progressed during treatment with 5-fluorouracil, doxorubicin, and mitomycin C (FAM) [22]. This patient then entered the current trial at level III and had stable disease after one cycle and complete disappearance of all measurable disease after three cycles. He developed dyspnea on exertion and treatment was discontinued; a complete reevaluation failed to demonstrate significant pulmonary toxicity. The patient was empirically treated with steroids for 1 month and all symptoms resolved. All drugs except intermittent prednisone were discontinued and he remained in complete remission for over 18 months.

Discussion

This study demonstrates that trifluoperazine can be given concomitantly with bleomycin to patients with cancer and that limiting toxicity was reached at a dose of 9 mg trifluoperazine b.i.d. This toxicity was neuropsychiatric, the most common symptoms being akathisia and depression.

Pulmonary toxicity was mild in two patients and fatal in one who had received a total of 270 IU bleomycin; thus, three of nine patients who received more than 120 IU bleomycin experienced pulmonary toxicity. Such an incidence of pulmonary toxicity, even in this older age group, is somewhat greater than expected [1]. The contribution of the phenothiazine to the pulmonary effects of bleomycin in man is not known. In previous studies in mice, we found no greater incidence of pulmonary fibrosis in animals receiving chlorpromazine with bleomycin than in those receiving bleomycin alone, as measured histologically and by the content of hydroxyproline [13]. In fact, at very high doses of bleomycin, chlorpromazine appeared to protect mice against the damaging effects of bleomycin [13]. In an ongoing phase II trial of trifluoperazine-bleomycin in the treatment of high-grade astrocytomas using 8 mg trifluoperazine b.i.d., 1 of 13 patients enrolled developed fatal, biopsy proven, pulmonary fibrosis after receiving only 150 IU bleomycin. Therefore, it is conceivable that in humans the combination is actually more toxic; further studies must be done to ensure its safety.

No measurable hematopoietic toxicity occurred in patients even at the highest dose of trifluoperazine, in contrast to our studies of the combination therapy on human hematopoietic precursors grown in culture, where significant myelosuppression was seen [13].

Four patients in the present study had measurable responses to therapy that lasted from 2 months to over 18 months. The responses were seen in three patients with mycosis fungoides and one with both mycosis fungoides and adenocarcinoma of unknown primary metastatic to the lung. Because mycosis fungoides is somewhat responsive to bleomycin, the contribution of the phenothiazine must await the results of phase III evaluations. However, since both trifluoperazine and bleomycin accumulate in the skin, it is also likely that this regimen is particularly suited for malignancies involving this site. Since adenocarcinoma is not sensitive to bleomycin and phenothiazines appear to be most effective in augmenting bleomycin in cell lines naturally resistant to the antibiotic, it is tempting to speculate that the effect of bleomycin was augmented by trifluoperazine.

This phase I study demonstrates that the maximum tolerated dose of trifluoperazine in the outpatient setting is <9 mg b.i.d. Using the same overall schedule, we have chosen a dose of 8 mg b.i.d. for a phase II trial of this combination against high-grade astrocytomas. In hospitalized patients, others have recently reported the use of up to 60 mg trifluoperazine daily in combination with doxorubicin [26].

We chose not to measure serum concentrations of phenothiazines in this trial since they have little, if any, correlation with pharmacological effect [25] due to their very large volume of distribution and the numerous active metabolites. Therefore, it is difficult to extrapolate the clinical dose to our previous in vitro studies. For example, our previous studies demonstrated a dramatic augmentation of the effect of bleomycin following 1-h exposure to 10–50 μM trifluoperazine [18]. A 16-mg dose of trifluoperazine would result in a total body concentration of approximately. 1 μM. Given the long half-life of this drug, it is likely that the cumulative dose of 64 mg would expose malignant cells to efficacious concentrations especially in the skin and CNS.

Impetus for the use of phenothiazines with other chemotherapeutic agents comes from the laboratory observations of Tsuruo and co-workers [28] and Ganapathi et al. [8], who have shown that phenothiazines and calcium channel blockers can sensitize multidrug-resistant cells to anthracyclines and vinca alkaloids. Miller et al. [26] have recently described the clinical use of trifluoperazine with doxorubicin in patients with resistant tumors; they found apparent sensitization, although differences in the schedule of doxorubicin might have contributed to these encouraging results. Our results indicate that doses of <9 mg trifluoperazine b.i.d. can be clinically used in combination with bleomycin in the outpatient setting. However, the dose of trifluoperazine found to be tolerated in combination with bleomycin should not be directly extrapolated for use with other chemotherapeutic agents, since unique toxicities may occur. We conclude that the combination of bleomycin with trifluoperazine is a potentially useful, new combination therapy deserving further clinical evaluation.

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