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ORIGINAL ARTICLE

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A phase I trial of high-dose oral tamoxifen and CHOPE

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Abstract Drug resistance is a common phenomenon in clinical oncology. In vitro, tamoxifen has been shown to be an effective inhibitor of P-glycoprotein and a modulator of the multidrug resistance phenotype. We have previously shown that vinblastine can be given safely in combination with tamoxifen at doses that may modulate P-glycoprotein activity. In this phase I trial, tamoxifen (150 mg/m^2 twice a day) was given with CHOPE (cyclophosphamide/doxorubicin/vincristine/prednisone/etoposide) in order to assess the toxicities of the combination. Resistance to three of these cytotoxic agents (doxorubicin, vincristine, and etoposide) may be mediated by P-glycoprotein. A total of 13 patients were evaluable on this trial, which showed that the maximum tolerated doses of cyclophosphamide and etoposide were 750 and 80 mg/m^2, respectively. The dose-limiting toxicity was myelosuppression with 50% of the patients (3/6) treated at this dose level developing febrile neutropenia and 85% (6/7) developing grade 4 neutropenia. Tamoxifen at a dose of 150 mg/m^2 twice a day can be given safely with the lymphoma regimen CHOPE at standard doses, but this combination may result in increased myelosuppression.

Key words Phase I trial · Tamoxifen · CHOPE · MDR modulation

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Introduction

Drug resistance is a common problem that limits the efficacy of chemotherapy. A major mechanism of antineoplastic drug resistance in vitro is active transport of chemotherapeutic agents out of cells, which is mediated by P-glycoprotein (Pgp) [13]. Increased expression of this 170-kDa membrane protein is associated with development of the multidrug resistance (MDR) phenotype, which is characterized by resistance to a number of naturally occurring antineoplastic agents. Pgp has been detected in a variety of tumor specimens [15], and its presence has been correlated with prognosis in childhood soft-tissue sarcoma [3] and neuroblastoma [4].

In vitro, a number of commonly used drugs, including verapamil [18], quinidine [19], cyclosporine [16], and tamoxifen [1], reverse the MDR phenotype through inhibition of Pgp. Most of these agents, however, are toxic at doses required to inhibit Pgp in vivo [14]. Tamoxifen is a possible exception. In a phase I trial of high-dose tamoxifen and continuous-infusion vinblastine [17], plasma levels of both tamoxifen and its primary metabolite, *N*-desmethyltamoxifen, sufficient to reverse MDR in vitro were achieved without major toxicity. The dose-limiting toxicity on this trial was neurotoxicity manifesting as gait instability, tremor, and dysmetria. No potentiation of hematologic toxicity was seen.

CHOPE (cyclophosphamide/doxorubicin/vincristine/prednisone/etoposide) is a five-drug combination that has been evaluated as a therapy for lymphoma [7, 9, 12]. This regimen contains three natural products (doxorubicin, vincristine, and etoposide), resistance to which may be mediated by Pgp. On the basis of data from the phase I trial of tamoxifen and vinblastine, we conducted a phase I trial of high-dose oral tamoxifen and CHOPE. The dose-escalation scheme for these agents was based on ongoing trials of CHOPE being conducted by Cancer and Leukemia Group B (CALGB) [12].

Patients and methods

Patients

Eligible patients with advanced refractory malignancies were required to have a performance status of 0, 1, or 2 (Eastern Cooperative Oncology Group criteria) and adequate bone marrow (granulocyte count, $\geq$1,500/mm^3, platelet count, $\geq$100,000/mm^3: hemoglobin, $\geq$9.9 g/dl), renal (serum creatinine, $\leq$1.8 mg/dl), and hepatic function (bilirubin, $\leq$1.9 mg/dl; serum glutamic-oxaloacetic acid transaminase, $<$4 times the normal value). Patients with known brain metastases were excluded, as were patients receiving any concurrent cancer therapy. No radiation therapy or chemotherapy was allowed in the 4 weeks preceding study entry (6 weeks for nitrosoureas or mitomycin C). All patients provided written informed consent prior to entry, and the study was reviewed by the Institutional Review Board of Duke University Medical Center.

Study design

The study was designed to assess the safety of administration of high-dose oral tamoxifen with CHOPE. Tamoxifen (ICI Pharma, Wilmington, Del.) at 150 mg/m^2 twice a day was given on days 1–10 of each cycle. CHOPE was started on day 8. All patients received doxorubicin given at 50 mg/m^2 X 1, vincristine given at 1.4 mg/m^2 X 1, and prednisone given orally at 100 mg qd X 5. Patients in the initial cohort were given cyclophosphamide at 400 mg/m^2 X 1 and etoposide at 50 mg/m^2 qd X 3. Cyclophosphamide doses were escalated in subsequent cohorts to 750 mg/m^2 for the second dose level and to 1,000 mg/m^2 for the third. The etoposide dose was increased to 80 mg/m^2 in both subsequent cohorts. Complete blood counts and serum electrolytes were monitored on a weekly basis unless grade 4 myelosuppression developed, in which case the blood counts were monitored three times per week. Treatment was repeated every 28 days and recovery from myelosuppression was required prior to retreatment. Patients with delayed recovery (up to day 35) were eligible for retreatment at 90% of their prior cyclophosphamide and etoposide doses, provided that their granulocyte count had reached 1,500/mm^3 and their platelet count was $\geq$100,000/mm^3. The tamoxifen dose was decreased by 50% in patients who developed neurotoxicity. Six patients were to be enrolled at each dose level; however, accrual was to be discontinued at any time when the maximum tolerated dose (MTD) was reached. The MTD was defined as the dose level at which $\geq$50% of the patients enrolled developed dose-limiting toxicity (DLT). DLT was defined as hospitalization for febrile neutropenia, grade 4 myelosuppression lasting for 7 days or more, or any other grade 3 toxicity other than alopecia that occurred during the first cycle of therapy. Toxicity was graded according to the Common Toxicity Criteria of the NCI. In patients in whom response could be assessed, standard criteria were employed.

Results

Between March 20, 1991, and March 10, 1992, 16 patients were registered for this trial. In all, 13 patients received therapy according to the protocol and were evaluable for the purpose of determining the MTD. Two patients who initially consented to the trial elected to receive other therapy, and another died of rapidly progressive disease prior to the start of tamoxifen treatment. A seventh patient was enrolled at the second dose level after one of the early patients was noncompliant in terms of obtaining his laboratory evaluation. The characteristics of the evaluable patients are summarized in Table 1. Nine patients had previously been treated with chemotherapy; five, with radiation therapy; and one, with hormonal therapy. Two patients had received no prior therapy.

Table 1 Patients' characteristics

Number of patients	13
M/F	8/5
Median age (range)	50.5 (20–74) years
Diagnoses:	
Adenoid cystic carcinoma	2
Renal-cell carcinoma	2
Prostate cancer	1
Cervical cancer	1
Lung adenocarcinoma	1
Adenocarcinoma of unknown primary	1
Melanoma	1
Ovarian cancer	1
Mucoepidermoid carcinoma	1
Germ-cell cancer	1
Median number of cycles (range)	2.5 (1–8)

As expected, the DLT was myelosuppression. None of the patients in the first cohort was hospitalized with febrile neutropenia, and none had prolonged myelosuppression despite the development of $\geq$grade 3 leukopenia in five of the six patients. Dose escalation was halted after the enrollment of the second cohort of patients since the criteria for the MTD were met at this level. Three of the six patients fully evaluable at this level were hospitalized with febrile neutropenia. Six of the seven patients treated at this level had grade 4 neutropenia and one patient had grade 3 thrombocytopenia. The remainder of the hematologic toxicities were mild and all patients had prompt recovery of their counts.

The median number of therapy cycles delivered was 2.5 (range, 1–8). Nine patients received more than one cycle; seven required reduction of the CHOPE dose for subsequent cycles. The maximal number of cycles delivered without a reduction of the tamoxifen or CHOPE dose was eight. The vincristine was held in one patient after he developed progressive peripheral neuropathy following three cycles of therapy, but all other reductions of the doses of cytotoxic agents were due to hematologic toxicity. Tamoxifen doses were reduced in three patients due to neurologic toxicity manifesting as dysmetria and alteration in coordination; this was the only other significant toxicity seen. An additional three patients reported mild gait unsteadiness consistent with the previously described neurotoxicity associated with high-dose tamoxifen. In all cases, this toxicity was documented prior to the administration of CHOPE. There was no evidence that the neurologic toxicity of the cytotoxic agents was increased by concurrent administration of tamoxifen.

A partial response was documented in one patient with a metastatic mucoepidermoid carcinoma, and minor responses were seen in two patients, one with an adenoid cystic carcinoma and one with adenocarcinoma of the lung. In the patient with adenoid cystic carcinoma, the response may have been due to tamoxifen itself, since there was

some decrease in the erythema and induration of his skin metastases during the tamoxifen loading period.

Discussion

B-cell neoplasms such as lymphocytic leukemias, non-Hodgkin's lymphoma, and multiple myeloma are typically responsive to initial chemotherapy. The most active regimens are combinations built on the observed activity of single agents. This strategy seeks to utilize the different mechanisms of action of the various agents to maximize response. Unfortunately, the majority of patients develop recurrent disease that is resistant to chemotherapy. Several strategies have been devised to overcome this resistance, including the administration of alternating cycles of non-cross-resistant agents according to the Goldie-Coldman hypothesis and the use of high-dose regimens with growth-factor support. It appears that this resistance is mediated at least in part by Pgp, and an alternative strategy is to use modulators of the MDR phenotype. In this study we used tamoxifen, an in vitro inhibiter of Pgp, in combination with CHOPE, a regimen containing multiple agents susceptible to exclusion from cells via Pgp.

As with most trials in which modulation of drug resistance is attempted, there was no clear evidence that Pgp activity was inhibited by tamoxifen on this trial. Trials at the University of Arizona [11] and Stanford University [20] have shown indirect evidence of modulation by verapamil and cyclosporine A, respectively. In these studies, tumors refractory to doxorubicin (Arizona) and etoposide (Stanford) showed some evidence of response when these agents were given with the modulator. This was interpreted to show that the modulator rendered some previously resistant cells susceptible to the cytotoxic agent. Measurements of normal tissue function may provide another indirect method of assessing Pgp modulation. Both the liver and the kidney are rich in Pgp, and it has been hypothesized that alterations in hepatic and renal function may be indicators of Pgp modulation. This hypothesis is supported by transient rises in serum bilirubin seen with cyclosporine. Changes in the pharmacokinetics of cytotoxic agents may also be related to these alterations in normal tissue function. Both renal and nonrenal clearance of etoposide is decreased by concurrent cyclosporine administration [10]. Similar changes in doxorubicin pharmacokinetics have been reported with concurrent verapamil treatment [8]. These findings are consistent with inhibition of Pgp in the renal brush border and bile canaliculi, but they do not prove the hypothesis. In the absence of methods to measure the cellular uptake of chemotherapeutic agents in tumor specimens pre- and post-therapy, this type of indirect evidence may be the best we can obtain. No alteration of hepatic or renal function suggestive of Pgp modulation was documented during this trial.

There was an increase in hematologic toxicity over that seen in patients with non-Hodgkin's lymphoma treated with CHOPE alone in a phase I trial [12]. It is probable that the heavily pretreated population enrolled on this trial simply had less tolerance to CHOPE than the patients with lymphoma treated on the phase I trial. However, a similar effect was demonstrated with the combination of etoposide and cyclosporine [20], and in a trial of high-dose intravenous progesterone with doxorubicin [5]. In the latter trial, no alteration in doxorubicin pharmacokinetics was demonstrated, leading the authors to suggest that Pgp activity may have been modulated in hematopoietic stem cells. Pgp expression has been associated with CD34, an antigen expressed on hematopoietic precursors in both normal [6] and leukemic [2] cells, raising the possibility of an effect of modulation on precursor cells in the bone marrow. The population of patients examined in the current trial was clearly too small for any conclusion to be reached concerning such an effect, but the finding of increased myelosuppression is consistent with this hypothesis.

At the phase II dose of 150 mg/m^2 twice a day, tamoxifen can be given safely in this population in combination with CHOPE at standard doses. Further evaluation of tamoxifen as a modulator of Pgp is ongoing.

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