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Research paper

A phase I/II trial of paclitaxel for non-Hodgkin's lymphoma followed by paclitaxel plus quinine in drug-resistant disease

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Patients with non-Hodgkin's lymphoma (NHL) recurrent after chemotherapy exhibit clinical characteristics compatible with the phenomenon of multidrug resistance (MDR) and frequently have detectable levels of P-glycoprotein (P-gp). Paclitaxel has been used in recurrent NHL with limited success. To test whether clinical resistance to paclitaxel can be reversed, we treated patients having paclitaxel-resistant NHL with paclitaxel plus quinine and measured the effects of quinine on paclitaxel pharmacokinetics. Eligible patients had recurrent and measurable NHL. Patients initially received paclitaxel, 120 mg/m^2 (dose determined by a phase I trial of paclitaxel plus quinine), as a 20–24 h infusion every 3 weeks until there was evidence of clinical resistance. Patients then received paclitaxel at the same dose rate plus oral quinine at a fixed dose rate of 400 mg three times each day. Paclitaxel pharmacokinetics were studied in each patient using paired samples from plasma obtained at the end of the 24 h paclitaxel infusion as an estimate of the steady-state drug level. Of 14 patients treated with paclitaxel alone, one patient obtained a partial response (7%). At the time of disease progession, one patient (same patient) obtained a partial response with paclitaxel plus quinine (7%). Steady-state paclitaxel levels were obtained in 12 patients. In 11 of 12 patients the steady-state paclitaxel level was substantially lower with the addition of quinine. The average ratio of end of infusion plasma levels (paclitaxel alone/paclitaxel plus quinine) was 0.6 (range 0.31–0.97) indicating a 40% decrease in paclitaxel levels with the addition of quinine (p=0.001). We conclude that paclitaxel given by this dose and schedule has modest activity in recurrent NHL. The addition of quinine to paclitaxel also has limited activity, but the combination did reverse paclitaxel resistance in one patient, adding support to the hypothesis that clinical drug resistance can be overcome with chemosensitizers in individual patients. Pharmacokinetic studies indicate that the reversal of drug resistance in this study cannot be attributed to changes in clearance of paclitaxel (which appears to increase with quinine), but more likely to the sensitization of lymphoma cells. [© 1998 Rapid Science Ltd.]

Key words: Drug resistance, non-Hodgkin's lymphoma, paxlitaxel, phase I/II, quinine.

Introduction

Paclitaxel has significant single-agent activity in a variety of solid tumors, but only modest activity in patients with previously treated non-Hodgkin's lymphoma (NHL).[1,2] Response rates have varied from 0 to 23% in 94 NHL patients reported.[3–5]

Patients with recurrent NHL exhibit clinical characteristics compatible with the phenomenon of multidrug resistance (MDR) and frequently have detectable levels of P-glycoprotein (Pgp).[6–8] We have previously shown that Pgp-associated MDR can be reversed *in vitro* using a variety of chemosensitizers[9–12] and that the relative effect of chemosensitization can be compared.[13] We, and others, have also demonstrated that acquired clincal drug resistance can be reversed in some patients using chemosensitizers.[8,10]

In the current study we test whether quinine can reverse acquired clinical drug resistance to paclitaxel by treating patients with paclitaxel-resistant NHL using paclitaxel plus quinine. Paclitaxel resistance *in vitro* can be reversed using pharmacologically achievable doses of quinine.[13] In fact, the relative *in vitro* chemosensitization of quinine on paclitaxel-resistant cell lines appears greater than that seen with other commonly used chemosensitizers including high-dose verapamil and cyclosporin A.[13] In the current study we also determine the effect of quinine on paclitaxel pharmacokinetics and the response rate of previously treated NHL to paclitaxel alone.

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Patients and methods

Phase I Component

Because of concerns from earlier trials that quinine might sensitize bone marrow stem cells to chemotherapy,[14] a small phase I trial of paclitaxel plus quinine was initially conducted to provide a limited toxicity profile for the combination and to establish the safety of the planned target doses. A starting dose for paclitaxel (Taxol®; Bristol Myers Squibb, supplied by the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD) of 135 mg/m^2 (level 1) was selected based on results with acceptable toxicity in patients with heavily pre-treated ovarian cancer.[15] Planned increases in paclitaxel (level 2, 155 mg/m^2, level 3, 175 mg/m^2) and decreases (level −1, 120 mg/m^2) were used in conjunction with a constant dose of quinine sulfate (400 mg, p.o., t.i.d., days 1–4) (200 mg tablets=160 mg quininebase; Warner Chilcott Laboratories, Morris Plains, NJ). Paclitaxel was administered on day 2 as a 20–24 h continuous i.v. infusion with the following pre-medication: dexamethasone, 20 mg given orally 12 and 6 h prior to paclitaxel; diphenhydramine, 50 mg given i.v. 30 min prior to paclitaxel; and cimetidine, 300 mg given i.v. 30 min prior to paclitaxel. Treatment cycles were repeated at 21 day intervals as peripheral blood counts allowed. Beginning with dose level 1, three patients were to be entered at each level. If one patient experienced greater than grade 2 toxicity, three additional patients were to be treated at the same dose level. If two of six patients experienced grade 3 or 4 toxicity, the next lowest dose level was to be designated the planned study dose for the phase II component. Patients of any histological type of cancer were eligible for this component.

Phase II component (two-stage design)

Patients were treated with paclitaxel, 120 mg/m^2, given as a 20–24 h continuous infusion. Pretreatment medications were given as described above. Patients with disease progression at any time, or no response following two cycles of paclitaxel alone, were treated with paclitaxel, 120 mg/m^2, given as a 20–24 h continuous infusion, day 2; and quinine, 400 mg given by mouth three times each day on days 1–4. Cycles of treatment were repeated at 21 day intervals until disease progression or no response after two cycles. Patients with biopsy proven, previously treated and recurrent NHL of any histologic type were eligible for this component. Standard Southwest Oncology Group (SWOG) definitions of response were used to determine disease progression (PD) and response [partial (PR) and complete (CR)].[16] Standard tests were used to determine the Ann Arbor clinical stage prior to treatment and to determine response following treatment.[16]

Patient selection

The minimum age for entry was 18 years (no upper limit specified). All patients had a SWOG performance status of 0, 1 or 2, an absolute granulocyte count $>2000/mm^3$, platelet count $>100000/mm^3$, pretreatment serum bilirubin <1.8 mg/dl and a serum creatinine <2.0 mg/dl. Specific exclusion criteria were as follows: clinical or laboratory evidence of central nervous system involvement with cancer; history of impaired cardiac status (including congestive failure or arrhythmia); concurrent need for heart medications; prior malignancy; and pregnancy. Patients of Southeast Asian or Black African descent were screened for glucose-6-phosphate (G-6PD) deficiency and G-6PD patients were ineligible. All patients were informed of the investigational nature of the study and gave written informed consent prior to enrollment in accordance with University of Arizona and federal guidelines. All clinical and regulatory aspects of this study were monitored and reviewed by Theradex (Bethesda, MD) for compliance and accuracy.

Pharmacokinetics procedures

Paclitaxel analysis by HPLC. Plasma samples were analyzed for paclitaxel levels using a reverse phase method modified after that of Rizzo *et al.*[17] The plasma sample (1.0 ml) was extracted with 5 ml of *t*-butylmethyl ether, centrifuged for 10 min at 2000 r.p.m., and the ether layer transferred and evaporated under an airstream. The residue was reconstituted with 1 ml of 40% (v/v) acetonitrile, vortexed and added to a C-18 Bond-Elut® column (Varian, Harbor City, CA), preconditioned with 2 ml acetonitrile and 5 ml of water. The column was washed with 2×200 µl of water and the paclitaxel was eluted with 5 ml of 70% (v/v) acetonitrile in water. This sample was again evaporated and reconstituted in 250 µl of mobile phase consisting of 45% (v/v) 0.02 M sodium acetate (pH 4.5), 55% acetonitrile. The flow rate of 2 ml/min was pumped isocratically on a Perkin Elmer (PE) Model 250 Biocompatible Binary Pump (Norwalk, CT). The 100 µl samples were injected using a autosampler

(Hitachi Model AS-200(R)) and paclitaxel was detected using UV absorbance at 227 nm (Model 1050 UV-VIS detector: Hewlet-Packard, Palo Alto, CA). All samples were injected twice and quantitation was performed using an external standard curve using peak areas (4.75 min retention time) integrated by the PE Nelson TurboChrome-4® program.

Paclitaxel protein binding. Standard curves were generated in human plasma with and without quinine added at a final concentration of 10 μg/ml. In addition, paclitaxel-spiked plasma samples were evaluated for binding to human serum albumin (0.05 g/ml) using ultracentrifugation through Amicon CentriFree® filters (Beverly, MA) with a cut off size of 30 000 Da. Again, samples were evaluated in the absence and presence of quinine, 10 μg/ml. Control experiments in the absence of plasma were performed to account for the binding of paclitaxel to the filter material.

Paclitaxel pharmacokinetics. The minimum detectable plasma paclitaxel concentration using this HPLC assay was 0.02 μmol/l. There was no interference from the addition of 10 μg/ml quinine (data not shown). In the paclitaxel-protein binding experiments, human serum albumin bound 61 ± 1.1% of a 1.0 μM paclitaxel solution incubated for 1 h at 37 C. The addition of 10 μg/ml quinine did not change this degree of protein binding. These experiments showed that quinine does not alter the detection or the degree of protein binding of paclitaxel *in vitro*.

It was assumed that plasma paclitaxel levels were at near steady state at the end of the 24 h infusion. Total body clearance was calculated by dividing the infusion rate by the steady-state paclitaxel concentration determined as the average of two levels obtained 15 min before and at the end of the 20–24 h infusion. The area under the plasma concentration curve (AUC) was then calculated by multiplying this mean infusion level by the 24 h infusion time as previously described by Jamis-Dow *et al.*[18]

Results

Phase I component

Ten patients were treated on the pilot safety phase of the study. Paclitaxel plus quinine resulted in grade 4 granulocytopenia (granulocytes < 500 cells/μl) in three of three evaluable patients treated at the starting dose (135 mg/m^2) resulting in two hospitalizations for neutropenic fevers. At the −1 dose level (120 mg/m^2 of paclitaxel), seven of nine patients had grade 4 granulocytopenia. At this dose there were 13 episodes of grade 4 granulocytopenia during 23 courses of therapy resulting in five hospitalizations among four patients for neutropenic fevers. All patients recovered rapidly and without problems. The neutropenia was short-lived and seldom delayed the next planned course, and, therefore, 120 mg/m^2 was chosen for the second phase of the trial.

Phase II component

Fourteen patients with NHL were treated with paclitaxel (120 mg/m^2) until evidence of lymphoma progression, or no evidence of a response after two cycles, followed by paclitaxel (120 mg/m^2) plus quinine. Clinical characteristics of the patient group are summarized in Table 1. One of 14 patients (7%) responded to paclitaxel alone and one of 14 patients (7%) responded to paclitaxel plus quinine (same patient). The single response to paclitaxel was seen in a patient with stage IV diffuse large cell NHL. Lung nodule masses and mediastinal adenopathy decreased greater than 50% over five cycles of paclitaxel, but progressed following the sixth cycle. The patient then received paclitaxel at an identical dose rate with quinine and achieved a second PR.

Paclitaxel pharmacokinetics

End of infusion (steady-state) paclitaxel plasma levels were obtained in 12 patients. Table 2 summarizes these levels and the converted AUC and clearance

Table 1. Clinical characteristics of 14 NHL patients treated with paclitaxel until clinical progression followed by paclitaxel plus quinine

Clinical characteristic	No. of patients (%)
Histology	
low grade	5 (36)
intermediate/high grade	9 (64)
Stage	
I–II	0
III–IV	14 (100)
Age	
<60 years	4 (29)
>60 years	10 (71)
Performance status	
0–1	10 (71)
2	4 (29)
Prior regimens	
⩽2	6 (43)
>2	8 (57)

Table 2. Plasma paclitaxel (T) pharamcokinetics with and without quinine (Q)

Patient no.	End of infusion concentration (μmol/l)		Total body clearance (ml/min m^2)		AUC (mm·h)	
	T	T+Q	T	T+Q	T	T+Q
1	0.183	0.254	534	384	4.39	6.10
2	0.449	0.327	185	254	10.76	7.84
3	0.164	0.050	595	1937	3.94	1.20
4	0.304	0.169	321	578	7.30	4.06
5	0.329	UD[a]	296	ND[b]	7.90	ND[b]
6	0.371	0.114	264	856	8.90	2.74
7	0.175	UD[a]	559	ND[b]	4.20	ND[b]
8	0.625	0.607	156	204	15.0	12.95
9	0.442	0.140	221	697	10.61	3.36
10	0.326	0.172	300	567	7.82	4.13
11	0.208	0.085	469	1245	4.99	204
12	0.132	0.060	739	1633	3.17	1.44

[a]Undetectable (<0.02 μmol/l).
[b]No determination possible.

values for the two courses (with and without quinine). In 11 of 12 patients, the steady-state paclitaxel level was substantially lower with the addition of quinine. On average, the ratio of plasma levels (paclitaxel alone/paclitaxel plus quinine) was approximately 0.6, indicating a 40% decrease in paclitaxel levels with quinine (p=0.001 by paired t-test). Indeed, in one patient a paclitaxel level was not detected after finishing the 24 h paclitaxel infusion with the oral quinine regimen. Using calculated paclitaxel clearance values from the 24 h levels, mean paclitaxel clearance increased from 386 (±186) ml/min/m^2 without quinine to 839 (±586) ml/min/m^2 when paclitaxel was combined with quinine (p=0.01 by paired t-test). This resulted in a commensurate decrease in the estimated mean paclitaxel $AUC_{(0-24)}$ from 7.41±3.53 to 4.55±3.59 μmol.h with the addition of the oral quinine.

Discussion

Our results confirm and extend findings of previous reports demonstrating limited activity of paclitaxel in patients with recurrent NHL.[3-5] With 14 patients treated, the observation of a single response is consistent with other reports. Published results of phase II tests of paclitaxel, considered together with this report, record 18 responses in 108 patients treated (17%). This degree of activity for treating NHL is relatively low compared to other single agents which have been found to be of value in combinations.[19-22]

The primary objective of this study was to test the chemosensitization effects of quinine on paclitaxel-resistant NHL based on *in vitro* tests using a doxorubicin-resistant, P-gp-expressing myeloma cell line.[13] Lehnert *et al.* have shown pharmacologically achievable doses of oral quinine to be a potent modifier of chemosensitization, whereas verapamil and cyclosporin A are effective only at concentrations not readily achievable in plasma.[13] To test the chemosensitization effect, we used a two-stage design wherein patients were treated with paclitaxel until there was clinical evidence of drug resistance and then retreated at the same dose rate of paclitaxel plus quinine. We observed a single response to the combination in a patient clearly resistant to paclitaxel alone as evidenced by CT scan measurements showing increasing tumor during paclitaxel treatment. Although the response rate to the combination is low (7%), limiting the usefulness of the combination for treating patients with NHL, our data suggest that in some NHL patients clinical drug resistance can be modified with chemosensitizers. Sarris *et al.* have previously reported no effect of cyclosporin A on clinical resistance to paclitaxel in 26 patients with paclitaxel resistance (although a single patient did achieve a partial response following the addition of cyclosporin A to paclitaxel).[23] They achieved cyclosporin A plasma levels of 2000 ng/ml, which is in the range Lehnert *et al.* found to be effective *in vitro*.

The response rate to paclitaxel alone and to paclitaxel plus quinine may have increased had a higher dose rate of paclitaxel been used. However, the dose rate of paclitaxel was chosen, and limited, by our findings of excessive myelosuppression during the phase I component of the study. Presumably, quinine is an effective sensitizer of bone marrow stem cells. Klimecki *et al.* have shown P-gp expression in leukocyte lines from normal bone marrow with moderate expression of MDR1 mRNA in granulocyte precursors.[24] If quinine is working through the P-gp mechanism, it might be expected to decrease marrow tolerance for a cytotoxic agent normally inactivated through the same mechanism. Recent clinical data from the SWOG support this observation. Gaynor *et al.* have reported a significant increase in life-threatening granulocytopenia for the combination of CVAD (4-day infusion of doxorubicin and vincristine with bolus cyclophosphamide and dexamethasone) when combined with oral quinine plus oral low-dose verapamil, compared to CVAD alone, or CHOP alone (bolus drug administration).[14] Thus, quinine's effectiveness as a chemosensitizer appears to be limited by bone marrow toxicity.

Pharmacokinetic data from this study reveal a surprising effect of quinine to decrease the AUC for paclitaxel. This was statistically significant using paired samples from patients treated with paclitaxel alone and, subsequently, with the same paclitaxel dose rate plus quinine. Thus, the apparent clinical chemosensitization seen in normal bone marrow stem cells and the reversal of paclitaxel resistance in one patient cannot be attributed to a pharmacologic interaction resulting in increased exposure to paclitaxel. In contrast, quinine enhanced paclitaxel clearance. This is opposite the effect of delayed metabolism of other cancer drugs which has been described as one mechanism of action for other chemosensitizers such as verapamil and cyclosporin A.[25,26] Our results also suggest that new chemosensitizers will have to be studied pharmacologically inasmuch as their effects on cytotoxic drug matabolism cannot be generically predicted. For example, paclitaxel is known to undergo enhanced metabolic clearance when combined with other drugs which induce hepatic microsomal enzymes such as anti-epileptics and glucocorticosteroids.[27] Quinine appears to interact with paclitaxel in the same manner. The major mechanism of elimination of paclitaxel is by hepatic conversion to the inactive 6-α-hydroxytaxol metabolite by human cytochrome P-450 2C8 enzymes.[28] The current results suggest that quinine may induce this enzymatic pathway. Overall, the end of infusion paclitaxel levels observed in the current study are comparable to those reported in trials without MDR modulators. Specifically, the mean end of infusion paclitaxel level of 0.309 ± 0.146 seen without quinine (Table 2) is similar to the levels of 0.23 ± 0.035 and 0.43 ± 0.14 reported for 24 h infusion doses of 135 and 175 mg/m^2, respectively.[29] In contrast, the end of infusion paclitaxel concentration with quinine in the current trial was 0.165 ± 0.169. This is substantially lower than that reported in a trial using an even lower paclitaxel 24 h infusion dose of 105 mg/m^2.[30] This suggests that the pre-quinine levels obtained in the current study, following a dose of 120 mg/m^2, are not outside the anticipated range based on prior pharmacokinetic studies. However, the end of infusion levels on the quinine-containing arm in the current study are substantially lower than anticipated from the literature.

In summary, paclitaxel appears to have modest activity in recurrent NHL. Paclitaxel combined with quinine is relatively ineffective. However, this study supports the hypothesis that clinical drug resistance can be overcome in some patients using chemosensitizers. Additionally, the effect of quinine in this study cannot be attributed to delayed metabolism. We plan to continue to search for more active sensitizers and select for optimal combinations using *in vitro* tests of drug resistance.

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