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CLINICAL TRIAL REPORT

Intensive anti-inflammatory therapy with dexamethasone in patients with non-small cell lung cancer: effect on chemotherapy toxicity and efficacy

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Abstract
Background Our preclinical and clinical data suggest that pretreatment with dexamethasone 4 days prior to chemotherapy increased the efficacy and decreased the toxicity of carboplatin and gemcitabine. To translate these findings to patients, we have undertaken a Phase 1/2 clinical trial.
Methods Thirty patients with advanced non-small cell lung cancer (NSCLC) received gemcitabine, 1,000 mg/m^2 on days 1 and 8, and carboplatin, AUC 5.5 on day 1. Patients were randomized (1:2:2) to receive, no dexamethasone (cohort 1), or oral dexamethasone at 8 mg (cohort 2) or 16 mg (cohort 3) twice per day, 4 days before and of the day of chemotherapy. Dexamethasone was administered to patients in cohorts 2 and 3 during courses 2–4.
Results In cohorts 1, 2, and 3, patients completing four planned courses of therapy were: 1/6, 6/12, 9/12. Partial responses (RECIST) were: 2/6, 6/12, and 7/12. Overall, dexamethasone significantly improved AGC and platelet nadirs and recovery times. There were no significant differences in non-hematologic toxicities between cohorts and no significant differences in pharmacokinetic parameters between course 1 and 2 in any cohort.
Conclusions These data support our previous preclinical and clinical observations that dexamethasone pre-treatment decreases hematopoietic toxicity and improves efficacy of this chemotherapeutic regimen in patients with metastatic non-small cell lung cancer and suggests that further randomized trials should be undertaken.

Keywords · Dexamethasone · Hematologic toxicity · Chemotherapy · Lung cancer

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Introduction

Despite advances in the development of new antineoplasitc agents, cytotoxic agents continue to be essential in the treatment of most human cancers. The major dose limiting toxicity of these agents is the development of neutropenia or thrombocytopenia, which can result in life threatening infections and bleeding [6, 13]. We have, therefore, pursued several lines of investigation to develop treatments to reduce the toxicity of these agents. The Phase 1/2 trial we report herein is based on observations from a series of preclinical studies in mice and a pilot clinical trial in cancer patients receiving carboplatin based therapy. We initially reported that pre-treating mice with cortisone acetate reduced the fatal hematologic toxicity of 600 mg/m^2 carboplatin from 80 to 15% in healthy mice and subsequently

in mice bearing syngeneic tumors [36, 38]. We also observed that hematopoietic stem cells from mice treated with cortisone acetate were resistant to cytotoxic effects of cisplatinum and radiation in vitro [36]. This latter observation raised the concern that pre-treatment with corticosteroids prior to cytotoxic chemotherapy could also induce tumor resistance to these agents as well. Therefore, we undertook a series of experiments to determine if dexamethasone, which we intended to use in clinical trials, demonstrated similar hematoprotective effects, and if dexamethasone induced tumor resistance to cytotoxic agents. Normal mice were pre-treated with dexamethasone for 4 days prior to 600 mg/m^2 of carboplatin. Dexamethasone pre-treatment reduced fatal hematologic toxicity from 80 to 10% at the optimal dose of 12 mg/m^2 [46, 47]. Using this pre-treatment dose and administration schedule we examined the effect of dexamethasone on antitumor activity of carboplatin, gemcitabine and doxorubicin in nude mouse-human xenograft models of breast, lung, colon cancer, glioma [47], and prostate (data not published) and in murine syngeneic breast cancer models [48]. In every model and tumor tested (a total of eight tumor lines), dexamethasone pre-treatment enhanced the antitumor activity of the chemotherapeutic agent in vivo. In these experiments, dexamethasone did not change carboplatin plasma pharmacokinetics, but reduced carboplatin AUC in normal tissue including bone marrow and spleen. Paradoxically the AUC in tumor tissue was increased by dexamethasone pre-treatment [47, 48].

The mechanisms by which pre-treatment with glucocorticoids reduces hematopoietic toxicity of chemotherapeutic agents in vivo and increase antitumor effects of the same agents has not been elucidated. However, dexamethasone has pleiotropic effects that suggest a number of non-competing mechanisms that may explain these differential in vivo responses between normal tissue and cancers. These include alteration in tumor and hematopoietic cell apoptotic pathways [17, 29–33, 35, 39, 40, 42, 48, 50], alteration in aberrant tumor vascular physiology [4, 5, 7, 8] and alteration in systemic vascular properties demonstrated in patients [12, 14, 18, 19, 26] and animal tumor models, e.g., tightening of leaky inter-endothelial capillary junctions induced by inflammatory cytokines of tumor origin [2]. However, in contrast to our preclinical results demonstrating that dexamethasone enhances chemotherapeutic efficacy, others have conducted in vitro and in-vivo preclinical studies that suggest dexamethasone attenuates the activity of anticancer agents [15–17, 33, 49, 51, 52]. The differences may be due to lower glucocorticoid doses and schedules used in those studies.

Based on data from our previously reported pilot clinical trial and our preclinical studies, we conducted and report herin a randomized Phase I/II trial designed to determine the optimal dose of dexamethasone pre-treatment to reduce chemotherapy hematopoietic toxicity. In the current trial, we chose to evaluate dexamethasone doses of 8 and 16 mg twice per day for 4 days before and on the day of chemotherapy. This is approximately 8 and 16 mg/(m^2 day) assuming a body surface area of 2. These doses were based on the following observations: (a) the optimal biologic dose of dexamethasone in mice to reduce carboplatin toxicity was between 12 and 36 mg/m^2 [46, 47], (b) the optimal dose to reduce tumor interstitial fluid pressure in rats was 9 mg/m^2 [26], (c) our previous pilot clinical trial demonstrated that 8 mg twice per day effectively reduced hematologic toxicity [37], and (d) our clinical experience with regimens such as VAD (vincristine, doxorubicin, and dexamethasone) suggested that single doses of 40 mg per day for 5 days given three times/month are near the maximum tolerated dose because of toxicities such as proximal muscle weakness, insomnia and others. In addition, preclinical studies in mice demonstrated that carboplatin induced hematologic toxicity was more effectively reduced with 3–4 day corticosteroid pre-treatment as compared to the 1 day pre-treatment [36, 38].

Patients and methods

Clinical methods and analysis

Patient eligibility

Eligible patients were required to have biopsy proven non-small cell lung cancer stage 3B with malignant pleural effusion or stage 4. Previous treatment was not allowed, except radiation therapy to <25% of the bone marrow for brain and sites of painful metastasis, or hemoptysis. Inclusion criteria required performance status 0, 1, or 2 with at least one measurable untreated site of disease by RECIST. Patients were required to have adequate hepatic, renal and bone marrow function as defined by serum bilirubin and creatinine $\leq$1.2 mg/dl. In addition, platelet, absolute granulocyte counts (AGC) and hemoglobin of $\geq$100,000/mm^3, 1,500/mm^3 and 8 g/dl were required. Patients that required use of corticosteroids, for any reason, and those that received corticosteroids within the previous 2 weeks prior to initial study treatment were excluded.

Baseline assessments

Complete history and physical examination, performance status determination, complete blood count and white blood cell differential (CBC), 12 component biochemistry profile (BP), and tumor measurements by computed tomography (CT) scans of all sites of suspected measurable disease (at

minimum of chest and abdomen). These evaluations were performed within 1 week of day 1 of treatment except CT scans, which were required to be within 2 weeks of day 1.

Study design and treatment plan

The objectives of this study were to evaluate (a) the relationship between dexamethasone dose and toxicity (hematologic and non-hematologic), and (b) dexamethasone dose and preliminarily tumor response to treatment. Primary endpoints of the study were the comparison between courses 1 and 2 of nadir AGC and platelet counts. Secondary endpoints were hematologic toxicities by comparison between courses 1 and 2 of total days with AGC <500 mm^3 and platelets $<20{,}000$ mm^3, recovery time after day 1 of treatment to AGC $\geq 1{,}500$ mm^3 and platelet count to $\geq 100{,}000$ mm^3, non-hematologic toxicities, tumor response and carboplatin and gemcitabine pharmacokinetics.

All patients were scheduled to receive four courses of standard intravenously administered chemotherapy consisting of carboplatin with an AUC of 5.5 mg $\times$ minute/mL on day 1 and gemcitabine 1,000 mg/m^2 on days 1 and 8 every 3 weeks. Thirty patients were randomized in three cohorts (6:12:12). Patients received no dexamethasone (all courses of cohort 1 and course 1 of cohorts 2 and 3), or dexamethasone in courses 2, 3 and 4 (cohorts 2 and 3). Dexamethasone was administered twice per day, 4 days before and the day of chemotherapy. Patients in cohort 2 received a total daily dexamethasone dose of 16 mg (in 4 mg tablets) and patients in cohort 3 received a total daily dose of 32 mg. Patients in cohorts 2 and 3 were not given dexamethasone in course 1 so that intra-patient and intra-cohort comparisons of toxicity endpoints could be made as well as inter-cohort comparisons.

Patients in cohort 1 in any course and patients in cohorts 2 and 3 during course 1 were not allowed to receive corticosteroids of any kind, but received standard antiemetics: pre-chemotherapy day 1, ondansteron 16 mg and lorazepam 1 mg intravenously and on day 8, ondansteron 8 mg intravenously. After course 1, doses of both carboplatin and gemcitabine were reduced 20% for the following toxicities: febrile neutropenia, documented infection associated with AGC ≤ 500 mm^3, platelets $\leq 10{,}000$ mm^3, bleeding when platelets were $\leq 50{,}000$ mm^3 and any grade >4 non-hematologic toxicity. Dose modification of dexamethasone was not allowed. Patients continued on treatment for four courses, unless cumulative dose reductions were $>40\%$, or disease progression was documented after course 2.

Study assessments

In all cohorts CBC were obtained on Monday, Wednesday, Friday while patients were on treatment. Prior to courses 2–4 all patients were evaluated with history and physical examination, determination of performance status, clinical toxicities, CBC, and BP. Prior to course 3 and 4 weeks after course 4, tumor measurements using CT scans of all sites of measurable disease were repeated.

Pharmacokinetics of carboplatin and gemcitabine were done on Day 1 of course 1 (no pre-treatment) and Day 1 of course 2 (pre-treatment with dexamethasone) on patients who consented to admission to the clinical research unit. Blood sampling times: carboplatin was infused from 0 to 30 min and gemcitabine was infused from 45 to 75 min. Blood samples were drawn prior to carboplatin dose, and at 15, 30, 35, 45, 60, 75, 80, 90, and 105 min, and 3.5, 6.5, 12.5, and 24.5 h.

Clinical data analysis and statistical considerations

Our choice to evaluate hematologic parameter changes was based on clinical relevance, but also on the accuracy as assessed by thrice weekly CBC. These included change between course 1 and course 2 in: (a) nadir platelet and AGC counts, (b) the time to recovery of peripheral blood counts to levels acceptable for the subsequent chemotherapy course, and (c) number of days that platelets were $<20{,}000/\text{mm}^3$ and AGC $<500/\text{mm}^3$. Since this trial was a Phase I/2 study and the primary objective was to determine the dose of dexamethasone to be used in future randomized studies, it was not powered to detect meaningful hypothesized differences between the two dexamethasone dose groups or the control group.

Formal hypothesis testing was performed by comparing mean differences and 95% confidence intervals in hematologic toxicity parameters and other biologic markers between courses 1 and 2. Only patients without chemotherapy dose change between course 1 and 2 were included in the analysis. These parameters were compared using paired, two sided Student's t test. Fisher's exact test was used to evaluate differences in response and number of courses completed between cohorts. Responses were assessed on intent to treat basis. Differences were deemed statistically significant when $P < 0.05$.

Responses were assessed on an intent to treat basis using RECIST criteria [44]. Toxicities were graded using CTC version 2.

Pharmacokinetic methods and analysis

Analytical methods

Previously published HPLC assays for measurement of carboplatin [47] and gemcitabine [9, 24, 45] from tissues and plasma were used for sample analysis following injection of calibrator solutions and quality control

samples. Daily system suitability checks to within 10% of nominal values were obtained prior to sample analysis.

Carboplatin was detected in microfiltrates obtained from centrifuged plasma (2000 × *g*) for 5 min in a Millipore Centrifree® micropartition cartridge. Analyte separation was achieved with a HPLC system fitted with a guard column (Waters Nova-Pak® C-18 guard column) and a LiChrosorb diol analytical column (10 mm; 250 × 4.6 mm. The mobile phase was acetonitrile:water (78:22; *v*/*v*) flowing at a 2 mL/min flow rate. Carboplatin was detected with an ultraviolet detector (229 nm). An external standard curve relating UV-detected peak area to carboplatin concentration was linear from 0 to 4,000 ng/mL.

Gemcitabine and its inactive metabolite, difluorodeoxyuridine (2dFdU), analysis was performed with an internal standard, 2′-deoxycytidine, method. Blood was drawn into heparanized tubes containing of deaminase inhibitor, tetrahydrouridine. Plasma was used for the analytical assay. Experimental samples were spiked with 20 μL of 165 mM aqueous 2′-deoxycytidine and mixed with 1 mL acetonitrile. Samples were centrifuged at 12,000 × *g* for 10 min and supernatants were dried under a nitrogen stream. Samples were reconstituted in 200 μL mobile phase, and injected onto a Waters Symmetry C-18 analytical column (5 mm; 250 × 4.6 mm) following a similarly packed guard column (20 × 3.9 mm). Gemcitabine, 2dFdU and internal standard were eluted with a mobile phase consisting of 50 mM ammonium acetate (pH 5.0): acetonitrile (96.5:3.5; *v*/*v*) at 1 mL/min and monitored at 280 nm with a UV detector. Concentrations of gemcitabine and 2dFdU in experimental samples were calculated from calibration curves relating analyte concentration to the ratio of analyte peak area and internal standard peak area.

Pharmacokinetic data analysis

Areas under the concentration-time curves (AUC) were obtained with non-compartmental analysis using WinNonlin v4.1 (Pharsight, Mountain View, CA). Nonlinear mixed effects analysis was done with NONMEM VI and PDxPop 2.0a (Globomax, LLC, Hanover, CT). Carboplatin data were fitted with a two-compartment model with the first order method with post hoc analysis. Gemcitabine pharmacokinetics were evaluated with a two compartment model and with a five-compmartment model to also fit the metabolite (2dFDU) data. A first order estimation method was used. All models used a proportional exponential error model to describe the inter-individual variability in the pharmacokinetic parameters. A proportional residual error model was used in all cases. Model selection was based on the goodness of fit plots, and minimization of the objective function value. The influence of dexamethasone treatment on clearance was assessed in each model. Population clearance was parameterized as follows to estimate the effect of dexamethasone dosage:

$$\begin{aligned}\mathrm{CL} = {} & \mathrm{Theta}\,(1) + \mathrm{Theta}\,(2) \times \mathrm{Dex} \times (\mathrm{Dex} - \mathrm{Arm}) \\ & + \mathrm{Theta}\,(3) \times \mathrm{Arm} \times \mathrm{Dex}\end{aligned}$$

$$\begin{aligned}&\text{Course 1; Cohorts 1 and 2: } \mathrm{CL} = \mathrm{Theta}(1) \\ &\quad \mathrm{Dex} = 0, \quad \mathrm{Arm} = 0; \quad \mathrm{Dex} = 0, \ \mathrm{Arm} = 0 \\ &\text{Course 2; Cohort 2: } \mathrm{CL} = \mathrm{Theta}(1) + \mathrm{Theta}(2) \\ &\quad \mathrm{Dex} = 1, \quad \mathrm{Arm} = 0; \\ &\text{Course 2; Cohort 3: } \mathrm{CL} = \mathrm{Theta}(1) + \mathrm{Theta}(3) \\ &\quad \mathrm{Dex} = 1, \quad \mathrm{Arm} = 1\end{aligned}$$

where dexamethasone had values of 0 (no dexamethasone) or 1, and cohort had a value of 0 or 1 to dictate the low and high dose dexamethasone treatment (i.e., cohort 2 vs. cohort 3).

A simpler model to test the effect of dexamethasone irrespective of the dexamethasone dosage was also used as follows:

$$\text{Course 2; Cohorts 2 and 3: } \mathrm{CL} = \mathrm{Theta}\,(1) + \mathrm{Theta}\,(2) \times \mathrm{Dex}$$

Similar parameterization was used to evaluate the effect of dexamethasone on other model parameters. The first order estimation (FO) method was used to build the structural models and for final analysis of the five-compartment model of gemcitabine and 2dFdU kinetics. A conditional method with Laplacian estimation was used for the final two-compartment models. To determine if dexamethasone or the dose level of dexamethasone pre-treatment were statistically significant covariates, we evaluated if their addition significantly reduced the two loglikelihood, which is related to the objective function value generated by NONMEM. For covariate acceptance into the model, a decrease in the objective function value of 10.83 with 1 degree of freedom was required and it indicates a significant difference ($p < 0.001$) based on the χ^2 test, or a 13.81 decrease is required to achieve significance with 2 degrees of freedom. The degrees of freedom were calculated by the difference in the number of parameters used in the full model and those in the base model. The change in the objective function value that we sought depended on the significance level we imposed.

Results

Patient demographics

Between May 2003 and March 2005, 30 patients were randomized to this study in a 1:2:2 ratio to cohorts 1, 2, and 3 (Table 1). All patients consenting to treatment under this

protocol were previously untreated for their lung cancer. Most patients were performance status 1, had adenocarcinoma, and were stage 4. There was an imbalance in sex between cohorts as 9 of 12 patients in cohort 2 were women, but this difference was not statistically significant compared to cohorts 1 and 3.

Hematologic toxicity

Figure 1a, b shows the platelet and absolute granulocyte nadirs. These data along with hemoglobin nadirs (data not shown) demonstrated relatively low intra-patient and intra-cohort variability. Interestingly, course 1 toxicity in cohort 1 was lower (higher nadir values), but did not reach statistical significance.

With respect to course 2, platelet nadirs were unchanged cohort 1 ($p = 0.22$), improved in cohort 2 ($p = 0.03$), and tended to improve in cohort 3 ($p = 0.07$). Similarly, AGC nadirs were not significantly changed in cohort 1 ($p = 0.88$), but improved in patients that received dexamethasone ($p = 0.02$ for both cohorts 2 and 3). Nadir hemoglobin declined in all cohorts during course 2 as compared to course 1, but less so in cohorts 2 and 3. The change in hemoglobin was: -1.5 ± 0.7(g/dL), ($p = 0.02$); -0.7 ± 0.6, ($p = 0.03$); and -0.5 ± 1.3, ($p = 0.22$).

Recovery after chemotherapy was also assessed by measuring the days required for platelets to return to 100,000/mm^3 and AGC to 1,500/mm^3 (Fig. 1c, d). As with the nadir data in course 2, these values appeared to worsen in cohort 1 and to improve in cohorts 2 and 3 (with dexamethasone), but these differences did not reach statistical significance.

After course 2 chemotherapy dose adjustments were allowed for those patients experiencing toxicity. The number of patients from cohort 1 that received four courses was not sufficiently high (1 of 5) to allow for subsequent evaluation of hematologic parameters (see below). However 6 of 11 patients in cohort 2 and 9 of 12 patients in cohort 3 received four courses of chemotherapy without dose adjustment. This allowed for comparison of the effect of two dexamethasone doses on platelet and AGC nadirs in all four courses. For AGC nadirs ($\times$ 10^3/mm^3) in cohorts 2 versus 3: Course 1: 0.9 ± 0.3 vs. 0.8 ± 0.3, Course 2: 2.0 ± 1.7 vs. 2.2 ± 1.4, Course 3: 2.3 ± 0.8 vs. 2.9 ± 0.7, and Course 4: 1.3 ± 0.4 vs. 3.5 ± 2.6. For platelet nadirs ($\times$ 10^3/mm^3) in cohorts 2 vs. 3: Course 1: 46 ± 29 vs. 34 ± 29, Course 2: 116 ± 69 vs. 92 ± 81, Course 3: 64 ± 39 vs. 57 ± 43, and Course 4: 27 ± 15 vs. 50 ± 39. Patients in cohort 3 appeared to have improved nadirs compared to cohort 2, but these differences did not reach statistical significance, for example, differences between cohort 2 and 3 in course 4 AGC and platelet nadirs were $p < 0.06$ and $p < 0.16$.

The incidence of other evaluated hematologic toxicity parameters was too infrequent for analysis including days of AGC <500/mm^3, and platelets <20,000/mm^3, red blood cell and platelet transfusions, antibiotic use and hospitalization for febrile neutropenia. The average number of hematologic adverse events reported in courses 1 and 2 were small ($\sim$1 or less/patient/course) for all cohorts. Although these numbers were lower in cohorts 2 and 3 during course 2, there was no statistical difference in adverse events per patient as compared to course 1.

Table 1 Demographics of patients evaluable for toxicity

	Cohort 1	Cohort 2	Cohort 3
Number of patients	5[a]	12	12
Age (median range)	57 (48–82)	66 (49–78)	64 (41–82)
Gender (M/F)	3/2	3/9	6/6
Performance status (ECOG)			
0	1	3	4
1	3	5	7
2	1	4	1
Histology			
Squamous	0	1	2
Adenocarcinoma	5	10	5
Large cell	0	0	1
NSCLC (not otherwise specified)	0	1	4
Stage			
IIIB	1	3	1
IV	4	9	11

Patients were evaluable for hematologic toxicity if they received any therapy

[a] One patient withdrew prior to any therapy

Non-hematologic toxicity

The incidence of non-hematologic toxicities (grades 1–4) was low (Table 2). Differences in the incidence of grades 3 and 4 toxicities were also low and not statistically significant among cohorts. The addition of dexamethasone in courses 2–4 in cohorts 2 and 3 did not increase the incidence of these toxicities and actually decreased (not statistically significant) in courses 2–4. However similar decline was seen in cohort 1.

Courses completed and reason for withdrawal from study

Sixteen of 30 randomized patients completed 4 courses of therapy (Table 3): 1 of 6 in cohort 1, 6 of 12 in cohort 2, and 9 of 12 in cohort 3. These differences tended toward but did not reach statistical significance. The major reasons for withdrawal were adverse events ($n = 7$), progressive

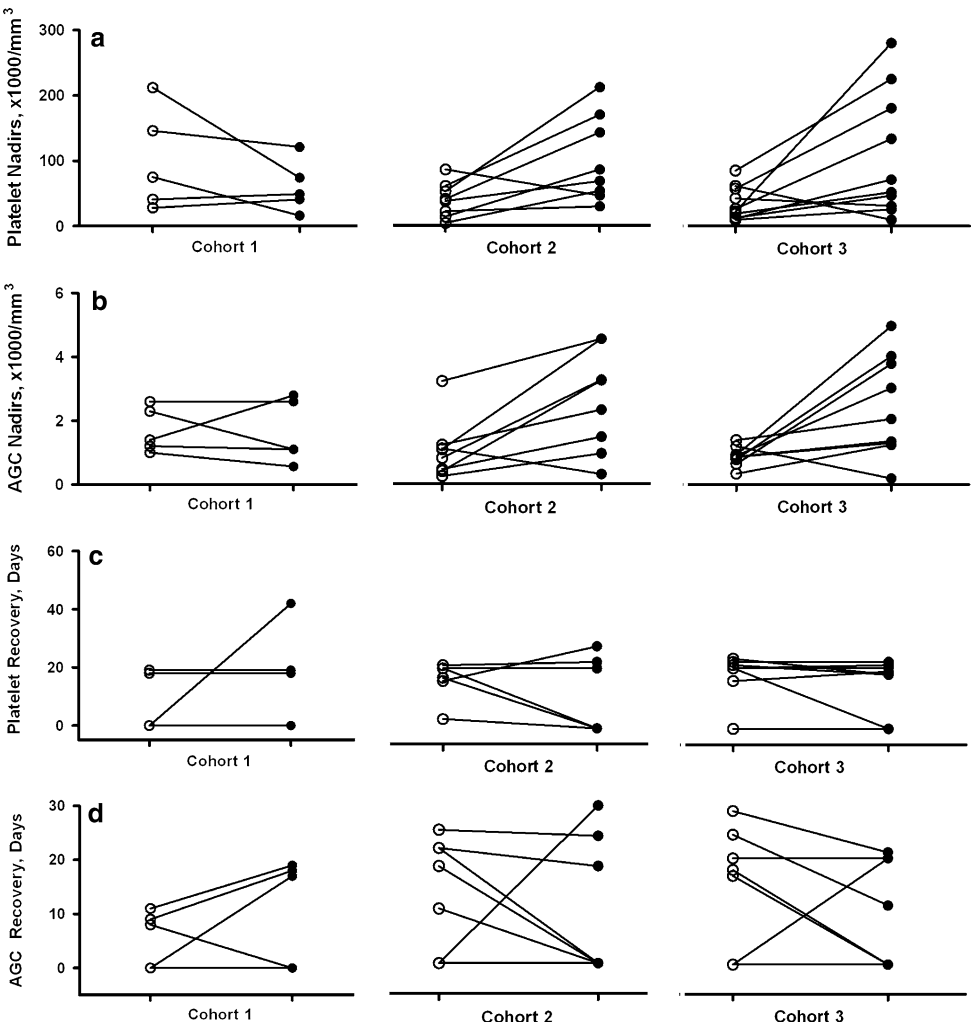

Fig. 1 Patients received the same dose of carboplatin and gemcitabine in courses 1 and 2. In course 1, patients received no dexamethasone. In course 2, patients received either no dexamethasone (cohort 1) or dexamethasone pre-treatment 8 mg (cohort 2) or 16 mg (cohort 3) twice each day for 4 days before and the day of chemotherapy. Nadir values for **a** Platelets and **b** AGC. Times to recovery for course 1 and 2 are shown for each patient. **c** Time to platelets of 100,000/mm^3, **d** Time to AGC of 1,500/mm^3. *Open symbols*, without dexamethasone; *closed symbols*, with dexamethasone. Note: recovery in (**c**) and (**d**) were 0 days if platelets and AGC were not less than the limits set above

disease after two courses ($n = 4$). One patient withdrew before receiving any therapy and one patient was withdrawn by the treating physician because of a decline in performance status.

Efficacy as assessed by response

Responses were determined on intent to treat basis. No complete responses were recorded, but overall partial responses were seen in 17/30 patients (Table 3). In two patients responses did not persist for 4 weeks so responses using RECIST criteria occurred in 15/30. Partial RECIST responses were observed in 2 of 6 patients in cohort 1, 6 of 12 patients in cohort 2, and 7 of 12 in cohort 3. These differences tended toward, but did not reach statistical significance.

Pharmacokinetics of carboplatin and gemcitabine

Non-compartmental estimates of the area under the time concentration curves were obtained for each patient who received carboplatin and gemcitabine during courses 1 and 2 from cohorts 1, 2 and 3 (see Figs. 2, 3). Potential differences in drug clearance that could arise from dexamethasone pre-treatment in course 2 were evaluated with non-linear mixed effects models using NONMEM. A two compartment structural model was used for the carboplatin and gemcitabine analysis. Gemcitabine pharmacokinetics were also evaluated with a five-compartment structural model [45] to test the effect of dexamethasone on the clearance of the 2dFdU metabolite. The five-compartment model was superior to a four-compartment model as assessed by the decrease in the objective function value from 1,119 to 1,093 ($p < 0.001$ based on the χ^2 test with 2 degrees of freedom). For all models, the clearance parameter was evaluated using covariate type coding with values of cycle 2 (with dexamethasone) being additive to the baseline clearance values. Initially, visual inspection of observed and predicted concentration versus time plots and residuals versus time plots were used to evaluate the base model (no dexamethasone covariates) and obtain appropriate initial estimates for each parameter. Differences

Table 2 Non-hematologic toxicity by course

	Cohort 1	Cohort 2	Cohort 3
Course 1			
All toxicities, total	33	57	49
All toxicities/patient	6.6	4.8	4.1
Grade 3/4 toxicities, total	5	5	3
Grade 3/4 toxicities per/patient	1	0.4	0.25
Course 2			
All toxicities, total	20	41	41
All toxicities/patient	4	3.7	3.7
Grade 3/4 toxicities, total	2	9	4
Grade 3/4 toxicities/patient	0.4	0.8	0.4
Course 3			
All toxicities, total	17	28	17
All toxicities/patient	5.6	3.5	1.8
Grade 3/4 toxicities, total	5	5	2
Grade 3/4 toxicities/patient	0.6	0.2	0.2
Course 4			
All toxicities, total:	2	18	26
All toxicities/patient:	2	3	2.9
Grade 3/4 toxicities, total:	0	4	8
Grade 3/4 toxicities/patient:	0	0.7	0.9

All data are recorded as the number of events, total for the cohort or per patient

Table 3 Courses of treatment completed and responses

	Cohort 1	Cohort 2	Cohort 3
Number of patients randomized	6[a]	12	12
Number of patients completing			
Course 1	5	12[b]	12[b]
Course 2	5[c]	11[d]	11[e]
Course 3	3[f]	8[g]	9
Course 4	1	6	9
Responses after two courses			
Progressive disease	2[h]	1[i]	1[j]
Stable disease	1	3	2
Partial response	2	6	8
Changes in response after four courses			
Progressive disease	1	1	1
Stable disease	0	0	0
Partial response	1	1	0
Total partial response	2/6	7/12[k]	8/12[k]

Reasons for incomplete treatment: [a]Patient withdrew consent. [b]Adverse event in 1. [c]Progressive disease in 2. [d]Progressive disease in 1, Adverse event in 2. [e]Progressive disease in 1. Adverse event in 1. [f]Physician decision due to poor tolerance to therapy in 1 and decline in performance status in 1. [g]Adverse event in 2

Reasons for no response assessment: [h]Patient withdrew consent. [i]One patient died of hematologic toxicity in Course 1 and was not assessed for response; one patient discontinued therapy after course 2 because of neuro-toxicity and was not assessed for response. [j]One patient withdrew after course 2 because of hepatic toxicity and was not assessed for response

Duration of responses: [k]One patient in Cohort 2 and one in Cohort 3 who developed a response after two course progressed after four courses

between the basic and covariate models were evaluated using the objective function value (OFV) with a decrease in the OFV of 13.81 points corresponding to a statistically significant improvement in the model fit ($p < 0.001$). None of the models reached this significance level. Typical values for reduction in the OFV were less than three units. Subsequently, a simpler model considering only the effect of dexamethasone was used (i.e., CL = theta1 + theta2 × DEX), but again the reduction in the OFV values did not reach significance by the inclusion of the additional parameter. More complex models that included similar parameterization on the volume and peripheral compartment parameters did not improve the model fit. Typical values for gemcitabine and carboplatin clearance are shown in Table 4 and were in accordance with published data.

As shown in Fig. 2, no obvious differences were observed in the concentrations or AUC values for gemcitabine and 2dFdU between course 1 and course 2 irrespective of the dexamethasone dosage. Patients in cohort 3 (course 2) had somewhat lower AUC for 2dFdU, but this difference was not statistically significant. Figure 3 depicts the carboplatin concentrations and resulting AUC values. Again, no obvious differences were observed between courses or cohorts, demonstrating that dexamethasone pre-treatment had no effect on the clearance of carboplatin in these patients. Typical estimates for the effect of dexamethasone on the clearance are also presented in Table 4.

Discussion

Although corticosteroids have been used in the treatment of cancer for many years, there has been no systematic study of their effect on hematologic toxicity, pharmacokinetics, or anti-tumor effects of chemotherapeutic agents. The results from the current study support our hypothesis that dexamethasone pre-treatment reduces chemotherapy induced hematologic toxicities. Hematologic toxicity as assessed by nadir AGC and platelet counts was reduced when patients were pre-treated with dexamethasone. Both nadir AGC and platelet counts improved significantly in course 2 (cohorts 2 and 3) with addition of dexamethasone whereas these parameters did not change or worsened in cohort 1 patients. Recovery times to AGC and platelet levels, which allowed initiation of the subsequent courses

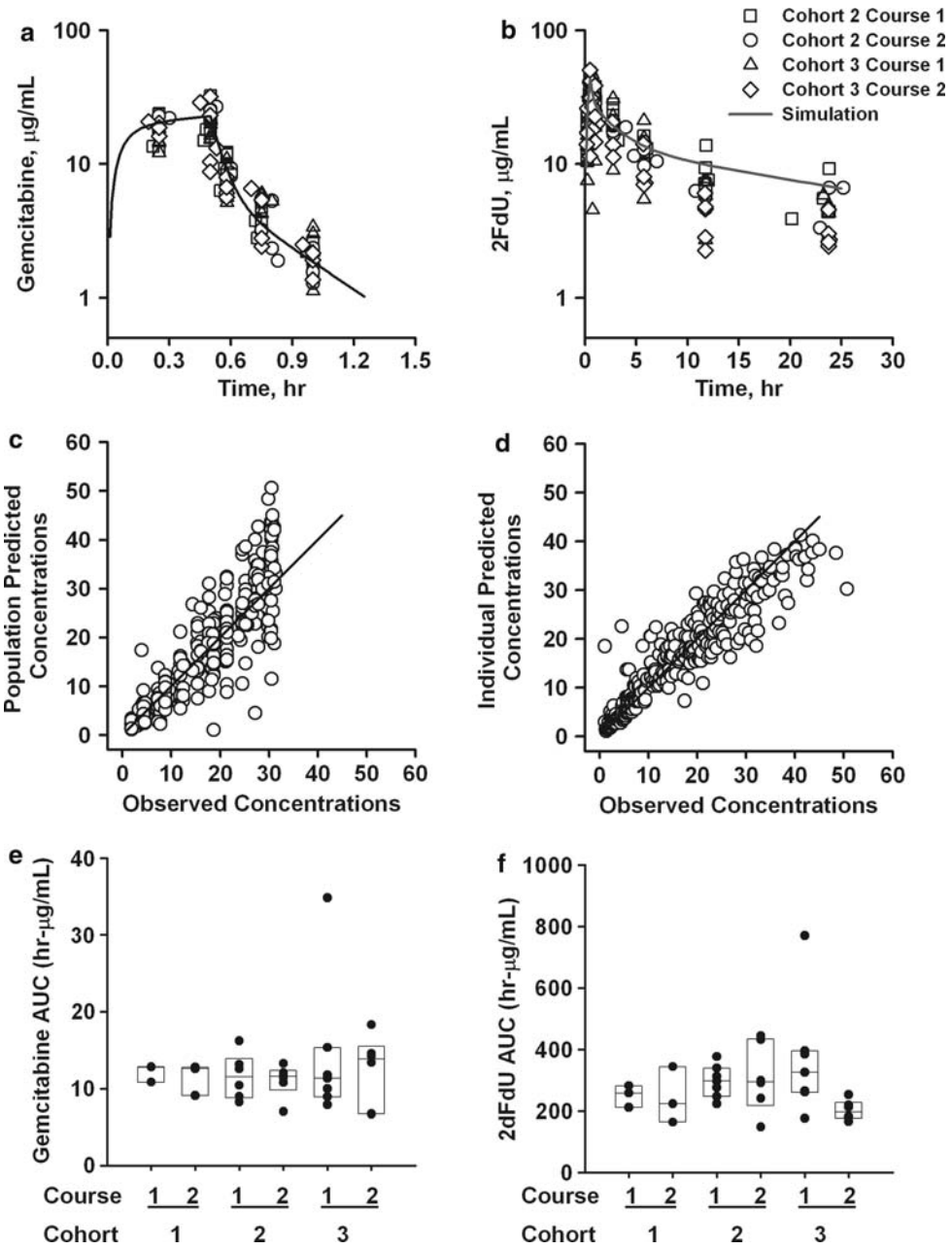

Fig. 2 Gemcitabine and metabolite (2dFdU) plasma pharmacokinetic profiles and simulated concentrations using non-linear mixed effects modeling. A five compartment structural model was used to simultaneously fit the gemcitabine and 2dFdU data. Gemcitabine plasma concentrations are displayed along with a simulated concentration profile for an individual receiving 1,000 mg/m^2 as a 30 min infusion (**a**). Plasma concentrations of 2dFdU from the same patients and a simulated concentration profile (**b**). Diagnostic plots for the population analysis depicting the observed data versus the model predicted population data (**c**) and the observed data vs. individually predicted data (**d**). Box plots and individual AUC values for gemcitabine (**e**) and 2dFdU (**f**)

of chemotherapy, also significantly improved in dexamethasone pre-treated patients. There was a trend toward reduction of CTC-3 defined adverse hematologic events with dexamethasone pre-treatment, although the overall incidence of hematologic adverse events was low and not significantly different among cohorts and courses.

Overall the pharmacokinetic parameters did not change between course 1 and course 2, irrespective of dexamethasone treatment. Drug exposure as measured by systemic clearance was similar to published data. Specifically, estimated carboplatin clearance was 9.57 L/h, which is very similar to the population clearance value (8.33 L/h) reported by Ekhart et al. in patients with normal kidney function [10]. A recent population analysis of gemcitabine pharmacokinetics reported clearance values of 162 L/h [22], but others have reported 90 L/h [34], which is closer to the estimated clearance, 85.0 L/h, in our patient population. Interestingly, patients in cohort 1 who underwent pharmacokinetic evaluation had a lower exposure to carboplatin in both course 1 and course 2 and this lower exposure was consistent with higher nadir AGC and platelet counts in course 1. Despite the lower exposure, these patients had lower nadir values during course 2.

Occurrence of non-hematologic toxicities was low and not significantly different between cohorts. There was a non-statistically significant trend for non-hematologic

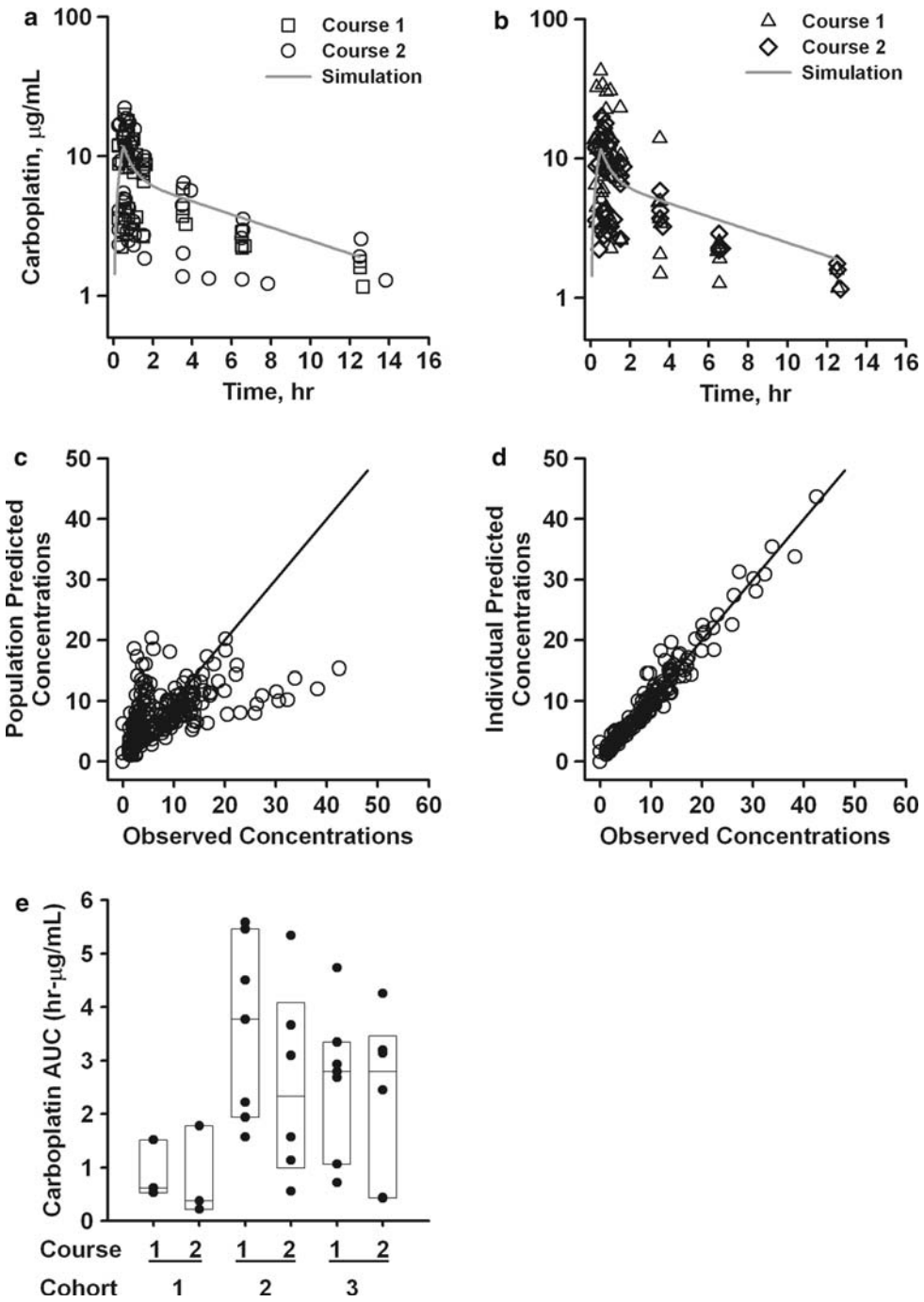

Fig. 3 Carboplatin plasma pharmacokinetic profiles and simulated concentrations using non-linear mixed effects modeling. Carboplatin plasma concentrations are displayed along with a simulated concentration profile for an individual receiving the average dose in these patients (1,200 mg) as a 30 min infusion. A two compartment structural model was used to fit the data for cohort 2 (**a**), and cohort 3 (**b**). Diagnostic plots for the population analysis depicting the observed data versus the model predicted population data (**c**) and the observed data versus individually predicted data (**d**). Box plots and individual AUC values for carboplatin (**e**)

toxicities to decrease in all three cohorts in course 2 (dexamethasone added in course 2 of cohorts 2 and 3) compared with course 1. These data suggest that the addition of dexamethasone did not add significant non-hematologic toxicity in cohorts 2 and 3. More dexamethasone pre-treated patients (cohort 2 and 3) compared to non-dexamethasone pre-treated patients received all four planed courses of chemotherapy (cohort 3 > cohort 2 > cohort 1). Tumor responses occurred more frequently in cohort 2 and 3 compared to cohort 1. These observations are consistent with our murine studies demonstrating improved tumor efficacy with dexamethasone pre-treatment.

We do not believe that our observations are due to altered plasma pharmacokinetics of carboplatin or gemcitabine since these were not significantly altered with addition of dexamethasone in course 2 in cohorts 2 and 3. We do not believe our observations are due to demargination of granulocytes by dexamethasone. The demargination effect of corticosteroids is transient lasting only 3–5 days and the

Table 4 The effect of dexamethasone and dexamethasone dosage on systemic clearance

Treatment	Estimate (L/h)	%RSE	95% Confidence Interval		
			Lower bound	Upper bound	IIV, % (%RSE)
Gemcitabine					
2-compartment model					
Base model (OFV = 277.5)	85.0	7.38	77.7	92.3	9.9 (124%)
Covariate model (OFV = 277.8)					
Without dexamethasone	84.8	–	–	–	–
With dexamethasone	84.9	–	–	–	–
5-compartment model					
Base model[a]					
Gemcitabine clearance	1.04	–	–	–	–
Apparent metabolite formation					
Clearance (CL_f/F)	82.6	–	–	–	–
Apparent metabolite clearance	2.95	–	–	–	–
Carboplatin					
Simple model (OFV = 594.8)	9.57	10.3	7.63	11.5	43.9 (36%)
Covariate model (OFV = 594.4)					
Without dexamethasone	9.01	11.8	6.93	11.1	34.4 (45.1%)
With dexamethasone	10.07	179	–	–	–

DEX *dexamethasone*; RSE *relative standard error of estimate*; IIV *inter-individual variability*

– indicates that values were not estimable

[a] No significant decrease in OFV or the clearance values were obtained with the covariate models tested

nadir AGC we observed occurred 11–14 days after dexamethasone was given. Moreover, dexamethasone had effects on hemoglobin and platelet nadirs (which are not demarginated by corticosteroids) and recovery times of platelets and granulocytes which occurred even longer after completion of dexamethasone administration.

We did not observe any dose limiting toxicities of dexamethasone at either the 8 or 16 mg doses so a maximum tolerated dose was not determined. However, the data suggest that the 16 mg dose is superior to the 8 mg dose: nadir counts and recovery times for platelets and granulocytes, the number of courses administered, and tumor responses all trended to or were significantly better in cohort 3 (16 mg) compared to cohort 2 (8 mg). Therefore we believe that the 16 mg dose administered twice per day (16/mg/(m^2 day)) is the recommended phase II dose.

The clinical data presented here are consistent with previous pre-clinical observations from our laboratories as previously discussed [36–38, 46–48]. Other investigators have also demonstrated the pre-treatment of mice with corticosteroids reduced hematologic toxicity of other chemotherapeutic agents [23, 25].

The results of our current study are consistent with previous clinical observations. We previously published a pilot clinical trial examining the protective effects of dexamethasone pre-treatment on hematologic toxicity [37]. This study was done in patients with metastatic cancer receiving carboplatin therapy and demonstrated that dexamethasone pre-treatment decreased hematologic toxicity [37]. The patient population in that pilot trial was heterogeneous but 60% were lung cancer patients and 6/12 patients pre-treated with dexamethasone developed a partial response while 3/16 patients who did not receive dexamethasone pre-treatment developed a response. Our data from the current and the pilot studies may explain the clinical observation that patients who are treated with the combination of paclitaxel, which requires dexamethasone pre-treatment, and carboplatin have less hematologic toxicity than those patients treated with carboplatin alone [1]. In this study by Belani et al. [1], patients who received paclitaxel in combination with carboplatin did not have altered carboplatin pharmacokinetics as compared to historical controls [3]. This is consistent with our current findings.

There may be several mechanisms by which corticosteroid pre-treatment reduces hematopoietic toxicity. We and other investigators have previously examined the in vitro sensitivity of bone marrow hematopoietic precursors to chemotherapeutic agents from untreated and mice treated with corticosteroids [23, 36]: hematopoietic precursors from corticosteroid treated mice were more resistant than those from untreated mice. These data demonstrating that hematopoietic stem cells exposed to dexamethasone in vivo have increased resistance to the cytotoxic chemotherapeutic agents in vitro may be explained by altered apoptosis although few studies have directly addressed this issue in normal hematopoietic cells [28].

Dexamethasone alters apoptosis of tumor cells and this effect may be tissue of origin, time of exposure and concentration dependent. In vitro most [17, 29, 30, 33, 35, 42,

49, 50], but not all [27] studies have shown that dexamethasone decreases chemotherapy induced apoptosis in epithelial cancers. In hematopoietic and lymphoid cancers dexamethasone has been demonstrated in most studies to induce or enhance chemotherapy induced apoptosis [17, 31, 39, 40, 50]. At least two studies have examined the effects of dexamethasone on paclitaxel efficacy in vivo, using human cancer-murine xenografts and demonstrated dexamethasone inhibition the anti-tumor efficacy [33, 42] of paclitaxel. However, these studies are not comparable to our murine or clinical data since the chemotherapeutic agents differed and the doses of dexamethasone used were 4–40 fold less than used in our studies.

Dexamethasone alters aberrant tumor physiology by decreasing inter-endothelial pore size, capillary fluid loss and as a result, decreases tumor interstitial fluid pressure which is abnormally elevated in epithelial cell tumors [5, 7, 12, 14, 18, 19, 21, 26]. These dexamethasone effects may offer an explanation for dexamethasone alteration of tissue pharmacokinetics observed in our studies: high tumor interstitial fluid pressure eliminates or reduces the gradient in pressure between capillaries and the interstial fluid space which in normal tissues favors delivery of solute into the interstial fluid space. We have also demonstrated that dexamethasone treatment of tumor bearing mice reduces tumor expression of VEGF and TNF (data not published) and dexamethasone reduces tumor interstitial fluid pressure. Thus both dexamethasone and anti-VEGF antibodies reduce levels of VEGF, decrease effective tumor interendothelial pore size, interstitial fluid pressure and improve drug delivery to tumors in experimental models [11, 20]. The mechanism(s) by which dexamethasone and cortisone acetate reduce normal tissue AUC of chemotherapeutic agents has not been demonstrated. We have proposed that in cancer patients, increased levels of pro-inflammatory cytokines induce increased capillary inter-endothelial pore size. In the absence of increased normal tissue interstitial fluid pressure, this may result in increased delivery of cytotoxic drugs to normal tissue, such as bone marrow, with resultant increased toxicity [43]. Corticosteroid therapy may decrease systemic levels of cytokines and reverse this process. However, vascular endothelial growth factor antibody (bevacizumab) in combination with carboplatin and paclitaxel treatment of metastatic non-small cell lung cancer has been shown to increase hematologic toxicity [41]. This suggests that lowering the level of a single cytokine (VEGF) may not be adequate to reverse this process.

This clinical trial and our previous pre-clinical studies [36–38, 46–48] support the hypothesis that pre-treatment of patients with lung cancer and other epithelial cell cancers with dexamethasone prior to chemotherapy will reduce hematologic toxicity and enhance efficacy. These results, if confirmed by appropriately powered randomized trials, have the potential to improve disease response rates in these patients. Insofar as responses are surrogates for overall and disease free survival, these outcomes may also be improved. Further, decreased hematologic toxicity may translate into improved drug delivery, improved quality of life and reduced cost of treatment by avoiding use of growth factors and hospitalizations for febrile neutropenia and infections.

To further develop this treatment strategy, we are currently undertaking a randomized Phase 2 trial powered to detect both significant reduction in hematopoietic toxicity and increase in overall response rates in patients with untreated stage 4 non-small cell lung cancer who receive carboplatin and gemcitabine. Patients are randomized to receive no dexamethasone or the optimal dose of dexamethasone, 16 mg twice per day for 4 days before chemotherapy.

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