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Deoxyspergualin: phase I clinical, immunologic and pharmacokinetic study

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Deoxyspergualin (DSG) is an analog of the polyamine spergualin with preclinical evidence of activity in murine and human tumor models. This phase I study examined a 120 h continuous infusion schedule in 56 patients with refractory solid tumors at doses ranging from 80 to 2792 mg/m^2/day. Dose-limiting toxicity was reversible hypotension and appeared to be associated with plasma levels of DSG > 4 μg/ml. Other dose-dependent effects noted were pruritus and circumoral paresthesias. Myelosuppression and gastrointestinal toxicities were mild and sporadic. Two patients with refractory head and neck cancer had minor responses. The recommended phase II dose on this schedule is 1800 mg/m^2. Additional monitoring to identify immunologic properties included immunophenotyping of peripheral lymphocytes and cytotoxic activity by means of standard ^{51}Cr-release assays. These studies revealed a non-dose-dependent increase in the number of cells expressing T cell antigens predominantly the T suppressor (CD8) phenotype post-treatment. In three patients, a mild increase in LAK activity was noted post-treatment without a consistent relationship to dose or change in cell surface antigens. Pharmacokinetic studies were completed on 26 patients ranging from doses of 80 to 2792 mg/m^2. The average plasma concentration ranged from 0.07 to 7 μg/ml. DSG was rapidly cleared from the plasma with a mean terminal half-life of 1.9 h. Mean total body clearance was 25.24 l/h/m^2. Further *in vivo* immunologic studies should be pursued while the agent is studied in fixed dosage phase II clinical trials.

Key words: Deoxyspergualin, pharmacokinetics, phase I trial.

Introduction

Deoxyspergualin (NSC-356894; DSG) is the 15-deoxy analog of the polyamine spergualin, a novel antibiotic isolated from culture broths of *Bacillus laterosporus*.[1,2] Spergualin is structurally related to spermine and is named after the spermidine and guanidine moieties in its structure (Figure 1). Direct comparison of the antitumor activity of spergualin and DSG by screening laboratories under contract to the NCI indicated both compounds had similar activity against the i.p.- and s.c.-implanted L1210 leukemia subline with DSG effective at lower doses. In addition, because of easier synthesis of DSG, it was selected over the parent compound for development in clinical trials. The mechanism of action is currently undefined.

Preclinical evaluation of DSG revealed good antitumor activity in L1210 and P388 leukemia models. This activity was found to be schedule-dependent with prolonged infusions optimal. The greatest therapeutic efficacy was observed by infusing 179 mg/kg/day for 72 h which produced an approximate 7-log reduction in tumor cell population.[3] The activity of DSG against drug-resistant P388 and L1210 leukemias *in vivo* demonstrated cross-resistance to cisplatin and L-PAM without cross-resistance to doxorubicin, vincristine, ara-C, methotrexate and cyclophosphamide. In addition, L1210 resistant to 5-fluorouracil was collaterally sensitive to DSG.[4]

Lethality studies were conducted in CD2F$_1$ mice. The 10% lethal dose (LD$_{10}$) on the single dose schedule was 31.5 mg/m^2. The LD$_{10}$ on 5 daily dose

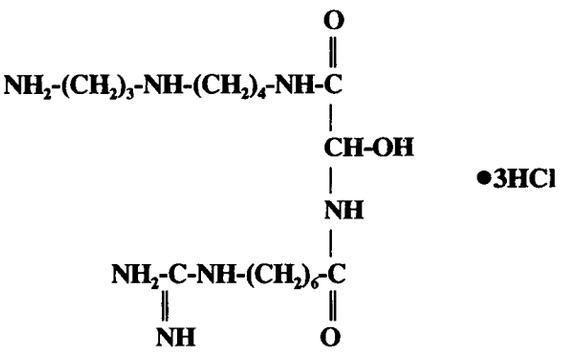

Figure 1. Structure of DSG ($C_{17}H_{37}N_7O_3 \cdot 3HCL$; MW: 496.9).

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schedule was 30.3 mg/m^2. Although the lethal doses were similar, the slope was much steeper for the 5 daily dose schedule. The LD_{90} on the single dose schedule was 47.4 mg/m^2 and on the 5 daily dose schedule was 35.7 mg/m^2. Animal toxicology conducted in beagle dogs on the 120 h continuous infusion schedule at 6 mg/kg/h demonstrated toxicity to the nervous (hypoactivity, tremors, ataxia, convulsions), urinary (hematuria, necrosis of bladder mucosa), gastrointestinal (emesis, mucosal necrosis), hematopoietic (anemia, leukopenia) and lymphatic systems. At the 2 mg/kg/h continuous infusion dose, only mild symptoms were seen without evidence of microscopic lesions noted in any system.[5]

Over the past several years, a variety of immunologic properties of DSG have been noted. In rat transplantation models, DSG has been shown to prolong allograft survival in heart,[6] liver,[7] kidney,[8] pancreas[9] and skin[10] transplants. Cardiac xenografts in primates have been successfully prolonged with DSG administration.[11] It has been shown to prevent graft versus host disease (GVHD) when given prophylactically[12] as well as ameliorate established GVHD.[13] In addition, DSG has inhibited the development of a variety of immunogically mediated diseases in animal models such as streptozotocin-induced diabetes,[14] experimental allergic encephalomyelitis[15] and lupus glomerulonephritis.[16] *In vitro*, DSG appears to have a biphasic effect on lymphocytes with proliferation stimulated at low doses but inhibited at high doses.[17] Other effects noted have been an increase in IL-2 production,[18] suppression of MLC reactivity,[19] and variable effects on IL-1 release and macrophage/monocyte function.[20,21] DSG appears to have a cytostatic rather than a cytolytic effect on bone marrow stem cells in murine models.[22]

This study, in addition to defining the toxicity of the compound, attempted to establish a possible mechanism for the dose-limiting toxicity as well as define selected *in vivo* immunologic characteristics at several dose levels.

Materials and methods

Selection of patients

All patients who entered onto this trial had histological confirmation of malignancy. Only patients with solid tumors refractory to all known forms of effective therapy with a predicted life expectancy of >12 weeks and a SWOG performance status of <3 were eligible. In addition, patients must not have received anticancer therapy for at least 3 weeks and must have completely recovered from any toxic effects of prior treatment. Measurable disease was not a requirement for entry onto this study.

Additional eligibility criteria included; (i) adequate bone marrow function (WBC >3000/mm^3, absolute granulocyte count >1500/mm^3, platelets >100,000/mm^3); (ii) adequate liver function (total bilirubin <1.5 mg%; alkaline phosphatase and serum glutamic-oxaloacetic acid transaminase <2-fold greater than normal); and (iii) adequate renal function (creatinine <2.0 mg%; creatinine clearance >50 ml/min; normal urinalysis). A recent myocardial infarction (<6 months) or uncontrolled ventricular ectopy or angina precluded therapy. As toxicity was observed, the eligibility requirements were amended to exclude patients with any history of a myocardial infarction, cerebrovascular accident, cardiac arrhythmia or a history of angina from participation in the study. Prior to entry, informed consent was obtained from the patient in accordance with federal and institutional policies.

Treatment plan

DSG was supplied by the NCI as a sterile powder in 100 mg single-use vials with 100 mg of mannitol. Each vial was reconstituted with 4 ml of sterile water for injection, USP, resulting in a solution containing 25 mg/ml of DSG. The dose of DSG was further diluted in 500 ml of 0.9% sodium chloride. Stability studies of the reconstituted, diluted product revealed no decomposition over 24 h at room temperature. Patients were hospitalized for all courses of treatment. The solution was infused over a 24 h period by an infusion pump repeated for a total of 5 days. This 120 h continuous infusion was administered every 28 days.

The starting dose of this trial was based on the toxic dose low (TDL) in the dog on the 5 day continuous infusion schedule which was 960 mg/m^2/day. One-third of the TDL was 320 mg/m^2/day; however, because of the small number of dogs treated at these doses, the starting dose was further reduced to 80 mg/m^2/day for 5 days. Three patients were entered at each dose level using the modified Fibonacci schema for dose escalation. An additional three patients were entered at a particular dose level if grade 3 or higher toxicity was encountered in any patient at that dose level.

Because of interesting immunologic data learned during the course of the trial and in an attempt to

identify a mechanism of action of the drug, additional patients were entered at 880 and 1719 mg/m^2 once the maximum tolerated dose (MTD) was determined. *In lieu* of pharmacokinetic studies in these patients, measurement of monoamine oxidase (MAO) inhibition in platelets and immunologic parameters was performed. These dose levels were chosen to determine dose-related effects. At 1719 mg/m^2 mild, asymptomatic hypotension was seen; at 880 mg/m^2 no hypotension was seen and, therefore, became a 'control'.

Study parameters

Prior to, during and for 24 h after the infusion, patients had frequent monitoring of their electrocardiogram (rhythm strip) and vital signs. Complete blood counts (including differential and platelets), chemistry profiles, prothrombin and partial thromboplastin times, creatinine clearance, and urinalysis were obtained prior to each course of treatment and monitored weekly for 4 weeks after therapy. A 12-lead electrocardiogram and chest radiograph were obtained prior to each course of treatment. Other laboratory and radiological examinations pertinent to tumor response were also performed prior to each course. Patients were followed closely for signs of toxicity or other biological effects. Standard response criteria of the Southwest Oncology Group were used to evaluate the antitumor effect of the drug.

Immunologic parameters

Immunologic studies included lymphocyte immunophenotyping and mononuclear cell cytotoxicity against cultured cell lines and fresh tumor targets. Blood samples for immunologic studies were obtained pre-treatment and 24 h into the 5 day infusion in two patients at 880 mg/m^2, three patients at 1719 mg/m^2 and the final patient at 2792 mg/m^2.

Mononuclear cells were isolated by density sedimentation on Ficoll-Hypaque as described previously.[23] Immunophenotyping was accomplished by incubating mononuclear cells with commercially available monoclonal antibodies to several cell surface markers including CD3, CD4, CD8, CD16 and Leu-19 (Becton-Dickinson, Mountain View, CA). The percentage of positive cells was analyzed by indirect immunofluorescence and flow cytometry.[23]

Cytotoxicity was assayed in a standard 4 h ^{51}Cr-release cytotoxicity system. Target cells included the standard natural killer (NK) target cell line, K562; the NK-resistant cell line, Daudi; and fresh tumor targets (breast). For the assay, target cells were washed and then incubated with ^{51}CR (200 μCi/5 $\times$ 10^{6}cells) at 37°C for 30 min to allow dissociation of loosely attached radioactivity and then washed a final time. Assays were performed using 5000 target cells. Effector cells (peripheral mononuclear cells) were added to achieve effector cell: target ratios of 80, 40, 10, 2.5 to 1. Parallel experiments contained target cells only or target cells plus 0.1N HCl to control for spontaneous ^{51}Cr release and to determine maximum ^{51}Cr release, respectively. All experiments were done in quadruplicate. Supernatants were harvested and counted in a Beckman Model 5500 gamma counter. Cytotoxicity was calculated by the following formula:

$$\frac{\text{c.p.m. released by effectors} - \text{c.p.m released spontaneously}}{\text{maximal c.p.m. released} - \text{c.p.m. released spontaneously}} \times 100$$

Pharmacokinetic sampling

Blood samples for pharmacokinetic studies were obtained on the first course of therapy from an indwelling i.v. heparin lock in the arm contralateral to the infusion line. Serial 8 ml specimens were collected in heparinized tubes before infusion, at hours 23, 24, 47, 48, 71, 72, 95, 96 and 119 during the infusion, at end of infusion, and 10, 20, 30, 45, 60 and 90 min, 2, 3, 4, 6, 8, 12, 23 and 24 h post-infusion. The collection times were amended during the study which deleted samples during the infusion except for the 96 h sample; post-infusion collections remained unchanged. Plasma was separated from whole blood by cold centrifugation, flash frozen and stored at −20°C in polyethylene tubes. A baseline urine specimen was obtained and serial 24 h urine samples were collected during and after infusion with the last collection period ending 24 h post-infusion. The total volume of each sample was recorded, the sample was shaken, and a 20 ml aliquot was removed, labeled and stored at −20°C.

HPLC Analysis

A modified reverse-phase HPLC assay utilizing post-column derivatization developed by Dr K. Yamashita (unpublished; Nippon Kayaku Company,

Tokyo, Japan) was used for the detection of DSG in urine and plasma. DSG reference standard was obtained from the Drug Synthesis and Chemistry Branch, Division of Cancer Treatment, NCI. The C_8-amide homolog of DSG used as the internal standard (IS) was a gracious gift from Dr K. Yamashita. Stock solutions and urine/plasma standard curves were prepared on the day of each procedure and all samples were assayed in duplicate. One milliliter of plasma or urine (diluted 1:100) was added to a 1.8 ml plastic microcentrifuge tube obtaining 1 μg of IS and 0.25 ml of pre-conditioned CM-Sephadex A-25 (Sigma, St Louis, MO). The bulk cation exchanger (CM-Sephadex), referred to as the 'column', was first washed with HPLC grade methanol followed by HPLC grade water, then activated with 0.1N NaOH followed by a water wash. Immediately following the addition of the plasma or urine, the mixture was gently rotated on an orbital shaker for 10 min and centrifuged for 20 s at 8000 r.p.m. The supernatant was discarded and the column washed twice with 1 ml of HPLC grade water. The absorbed DSG was eluted by adding 0.5 ml of 0.5 M NaCl and gently mixed on an orbital shaker for 1 h at 4°C, then centrifuged for 20 s at 8000 r.p.m. The supernatant was filtered through a 0.45 μm filter and 100 μl injected (WISP Model 710B, autosampler; Waters, Millford, MA) onto a C_{18} radial compression cartridge (μBondapack, 10 μm, 8 mm × 10 cm., Waters) preceded by a μBondapack C_{18} precolumn Guardpak (Waters). The mobile phase consisted of 20 mM sodium phosphate (pH 3): acetonitrile (81:19) containing 5 mM sodium heptanesulfonate pumped (model 510; Waters) at a flow rate of 3 ml/min. An *o*-pthalalelehyde (OPA) solution (0.7 g/l OPA), 1% methanol, 0.02% 2-mercaptoethanol, 0.1% (Brij 35) prepared in a 0.5 M potassium borate buffer (pH 10.7), at a flow rate of 0.5 ml/min, was used for the post column derivatization of DSG. Detection of DSG was by fluorescence with excitation set at 338 nm and emission at 455 nm. Standard curves constructed in blank donor plasma and urine were linear ($r^2 = 0.99$) over the range of 0.063–8 μg/ml.

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated using model-independent methods.[24] The terminal rate constant (k) was determined by log-linear analysis of the terminal phase of the plasma concentration versus time curves. The terminal plasma half-lives at the dosage level of 880 mg/m^2 and greater were calculated by the equation $t_{\frac{1}{2}} = 0.693/k$. Clearance was calculated by dividing the rate of the DSG infusion by the average steady-state plasma concentrations achieved during the 120 h infusion. The fraction of DSG excreted in the urine was estimated by dividing the average amount of DSG excreted in the urine over a 24 h period by the total dose received.

Termination of study

Individual patients were taken off study if objective tumor progression occurred or if they developed intolerable and/or life threatening toxicity. The phase I study was terminated when the MTD was established. The MTD was defined as the dose at which reversible grade 3 or greater toxicity was noted in four of six patients.

Results

Fifty-six patients with refractory solid tumors were entered on this study. All patients were evaluable for toxicity. Patient characteristics are outlined in Table 1. One hundred thirty-nine courses of DSG were administered at doses ranging from 80 to 2792 mg/m^2/day.

Table 1. Patient characteristics

Characteristics	No. of Patients
Total patients	56 (139 courses)
Median age (range)	61 (29–78)
Sex (M/F)	46/10
Performance status	
0–1	44
2	10
3	2
Previous therapy	
none	7
radiation only	8
chemotherapy only	16
radiation+chemotherapy	24
biologics (IL-2, interferon)	1
Type of tumor	
lung (non-small cell)	15
colorectal	10
head and neck	7
breast	4
lung (small cell)	4
renal	5
unknown primary	4
others[a]	7

[a] Melanoma, bladder, gastric, sarcoma, sertoli cell.

Dose-limiting toxicity—hypotension

Hypotension, both systolic and diastolic, was dose-limiting at 2792 mg/m^2 in five of six patients. The maximum percent decrease in systolic blood pressures from baseline was 25–44%. The onset of the hypotension varied among patients and occurred from 4 to 18 h into the infusion. The hypotension resolved in all patients within 1–8 h after discontinuation of the drug. The drug was discontinued in three patients as a result of the hypotension. In two others, administration of i.v. fluids allowed completion of a full course of therapy without untoward effects. One patient consented to rechallenge with the agent and experienced hypotension at a similar point into the infusion as with the initial course. There were no chronic sequelae directly related to the hypotensive episodes. Figure 2 plots the change in systolic blood pressure and plasma concentrations over time for a patient receiving their first 24 h infusion of DSG (2792 mg/m^2) until discontinued due to hypotension. This patient's end of infusion plasma level was 6 μg/ml. All patients at 2792 mg/m^2 with hypotension had peak or end of infusion plasma concentrations of 4 μg/ml or higher (See Table 2). The final patient treated at the 2792 mg/m^2 dosage level was prehydrated with 2 l of normal saline in an attempt to ameliorate the hypotension. This patient also experienced hypotension within 6 h of beginning the infusion. No

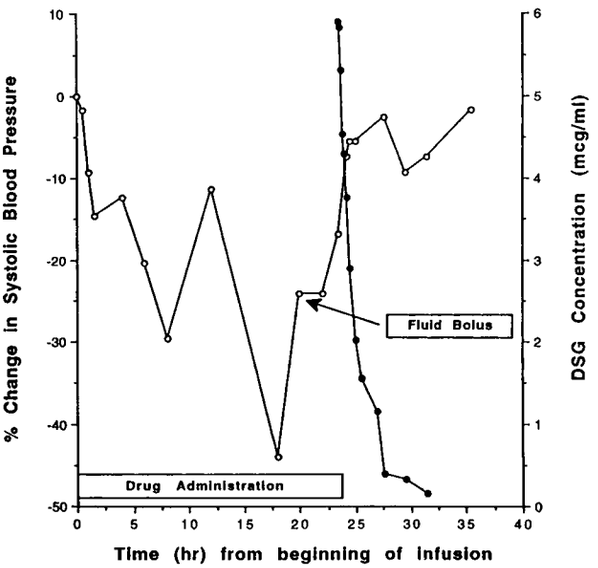

Figure 2. Percent change in systolic blood pressure versus plasma concentration of DSG over time in one patient at 2792 mg/m^2 (○, percent change of systolic blood pressure; ●, DSG concentrations).

Table 2. DSG pharmacokinetic parameters

Dose (mg/m^2)	No. of patients	Cp_{ave} (μg/ml)	Clearance (l/h/m^2)
80	1	0.07	47.49
160	2	0.20	36.14
264	2	0.41	28.54
400	2	0.69	24.39
560	3	0.77	30.54
720	1	1.03	29.13
880	2	1.69	22.22
1110	2	2.43	18.89
1375	3	2.40	26.03
1719	2	4.01	17.90
2148	1	3.89	23.01
2792	5	7.02	16.95

hypotension was seen at the 2148 mg/m^2 dosage level. At the 1719 mg/m^2 dosage level a retrospective review of the records revealed asymptomatic decreases in blood pressure in two of the four patients.

Because of preclinical information noting the antiproliferative effects of the parent compound spergualin were dependent on the presence of amine oxidase in the serum,[25] an attempt was made to correlate levels of MAO inhibition with hypotension. Inhibition of MAO in platelets was measured as previously described.[26] Blood samples were obtained from seven patients (three at 880 mg/m^2, three at 1719 mg/m^2 and one at 2792 mg/m^2) pretreatment and 24 h into the infusion, except in two patients in whom blood was obtained at completion of the 5 day infusion. Overall there was no significant difference in inhibition of MAO after treatment with DSG. Two patients were noted to have a 20–30% inhibition of MAO activity: one patient at the 880 mg/m^2 dose level and one at the 2792 mg/m^2 dose level. Symptomatic hypotension was documented in only one of these patients at the highest dose level.

Other toxicity

At the 2792 mg/m^2 dose level, six of seven patients complained of circumoral paresthesias which began 1–2 h into the infusion. Two patients noted more generalized paresthesias involving extremities. One patient related episodes of slurred speech to the degree of dysesthesia involving her mouth. Agitation and severe headache was noted in one patient at the highest dose level. This patient was subsequently found to have brain metastasis with marked cerebral edema. Pruritis was present in four

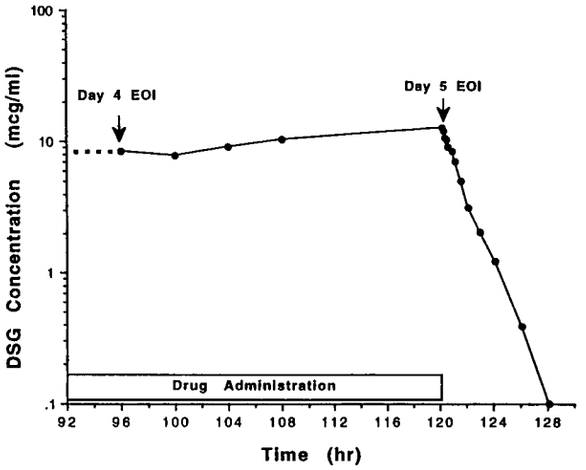

Figure 3. Representative plasma concentration over time of DSG in a patient receiving a continuous infusion of DSG at the 2792 mg/m^2 dosage level (EOI, end of infusion).

of seven patients at 2792 mg/m^2 and was poorly controlled with hydroxyzine–HCl and cyproheptadine–HCl. Nausea and vomiting was sporadic and mild throughout the study. Hematologic toxicity consisted of sporadic thrombocytopenia (grade 1 at the highest dose; grade 2–3 in an occasional patient at lower doses) and leukopenia (grade 3 in one of seven patients at the highest dose; grade 2 in occasional patients at lower doses). At doses of 720 mg/m^2 and below, no hematologic toxicity was seen. One patient at 880 mg/m^2 experienced an upper gastrointestinal bleed with a diagnosis of gastritis on endoscopy. This patient also had sepsis from a urinary tract infection on presentation with the upper gastrointestinal bleed. There was no neurologic toxicity noted at doses below 2792 mg/m^2 except for one patient at 1719 mg/m^2 who complained of mild perioral paresthesias. There were no drug-related changes in serum chemistries in any patient during this trial.

Pharmacokinetic results

The average steady-state concentrations and plasma clearances for DSG obtained from 26 patients at doses ranging from 80 to 2792 mg/m^2 are summarized in Table 2. Figure 3 shows a representative plasma concentration versus time curve of DSG for a patient receiving 2792 mg/m^2 of DSG as a continuous infusion. Steady-state concentrations were rapidly achieved followed by a rapid decline in the plasma concentration. The harmonic mean terminal half-life of DSG was 1.9 ± 1 h with a mean total body clearance of 25.24 ± 8.6 l/h/m^2. A linear relationship ($r^2 = 0.93; p < 0.002$) was observed between the steady plate plasma concentrations and dose. Approximately $13.45 \pm 5.3\%$ of the total dose of DSG was excreted unchanged in the urine.

Immunologic results

Immunophenotype analysis was completed pre- and post-treatment in six patients. A small increase number of cells expressing T cell antigens post-treatment was noted within the most predominant increase in the T suppressor (CD8) phenotype. There was no overall increase in the NK cell population, B cell subsets or cells expressing the Fc receptor.

Cytotoxic activity as described above was accomplished in these same six patients. NK cytotoxicity was not affected by treatment with DSG. However, in three patients a mild increase in LAK activity was noted post-treatment (Figure 4). This increased activity was not dose-related, and no consistent rela-

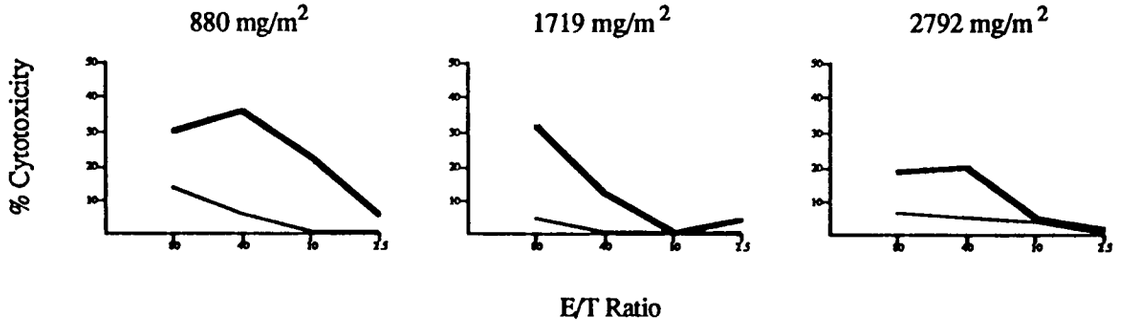

Figure 4. LAK activity in three patients receiving three different dose levels. Graphs represent percent specific lysis of Daudi (LAK) target cells calculated for a 4 h ^{51}Cr-release assay at four different effector:target ratios (80, 40, 10 and 2.5). Fine rule, pre-Rx; thick rule, post-Rx.

tionship between increased LAK activity and change in cell surface antigens could be demonstrated. Both NK and LAK cytotoxicity after incubation with IL-2 was not affected by DSG treatment (data not shown).

Tumor responses

Minor responses were noted in two patients with refractory squamous cell of the head and neck (41 and 44% decrease in soft tissue masses) of 3 and 4 months duration at doses of 160 and 880 mg/m^2, respectively. One patient with adenocarcinoma of the lung had a 30% decrease in pulmonary infiltrate of 2 months duration at 160 mg/m^2. One patient with biopsy-proven recurrent small cell lung cancer had stable disease for 14 months on therapy at doses of 80 and 264 mg/m^2.

Discussion

This phase I study of a 120 h infusion of DSG, an antitumor antibiotic, revealed the dose-limiting toxicity of this agent to be reversible hypotension. Other dose-dependent toxicities noted were pruritus and circumoral paresthesias which were most predominant at the MTD of 2792 mg/m^2. Other toxicities, in particular myelosuppression and gastrointestinal toxicity, were mild and sporadic in nature. These results are similar to a preliminary report of a phase I study of DSG examining a 3 h infusion daily for 5 days.[27] Dose-dependent toxicities of tongue and perioral numbness, hypotension, and mild nausea/vomiting were reported in that trial. Dose-limiting toxicity, however, was myelosuppression and perioral numbness with an MTD of 500 mg/m^2/day on that schedule.

The pharmacokinetic parameters of DSG characterized in our study are very similar to those reported by Muindi and colleagues.[28] Twenty-five patients receiving 80–2160 mg/m^2 of DSG for 5 days by continuous i.v. infusion obtained mean steady-state plasma levels of DSG ranging from 0.1 to 4.3 μg/ml. The terminal half-life at doses of 960 mg/m^2 or above was 1.9 h with a mean total body clearance of 22.1 l/h/m^2. Less than 10% of the administered dose was excreted as DSG.

During the course of the study an attempt was made to define a possible mechanism for hypotension, i.e. MAO inhibition. There was no correlation between hypotension and levels of MAO inhibition, possibly because of the small number of patients tested with only one of the patients at the MTD. There are several reports of the enhanced production of IL-2 in DSG treated animals.[29] Although levels of IL-2 were not measured, it is possible to postulate that the hypotension seen was in some way related to IL-2 or other cytokine production.

In this regard, interesting data has emerged regarding immunosuppressive properties of DSG. The present study, however, was unable to document consistent immunologic changes or biologic response modification by the methods we chose to study. One explanation for this lack of activity in the face of volumes of positive preclinical *in vivo* data may be the doses at which these studies were performed. It is clear that in animal models, doses revealing immunologic effects were below the initial starting dose of this phase I study. Interestingly, the patient with small cell lung cancer with stable disease for 14 months while on study began treatment at the initial dose level of 80 mg/m^2 with two dose escalations during the course of treatment. The three minor responses were seen at doses less than or equal to 880 mg/m^2.

The phase II recommended dose of DSG on this schedule is 1800 mg/m^2. It is based on the lack of symptomatic hypotension seen at 1719 mg/m^2 dose. Selected phase II studies should be completed in tumors shown to have preclinical sensitivity or suggestions of response in phase I trials such as breast or head and neck cancer. The real value of this new agent may not be as an antineoplastic but as an immunosuppressive agent in the transplantation setting. Although DSG has properties comparable to cyclosporine A, there are distinct differences in IL-2 production and effects on T cell functions.[18,19] Studies of its immunosuppressive properties at doses comparable to those studied in animal transplantation models should be pursued.

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