Phase I Trial Using Adaptive Control Dosing of Hexamethylene Bisacetamide (NSC 95580)¹

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ABSTRACT

Hexamethylene bisacetamide (HMBA), a potent differentiating agent, was administered to patients with refractory malignant tumors. Thirteen patients received 30 evaluable courses. HMBA was given by continuous i.v. infusion for 5 days. Therapy was repeated every 28 days, if patients had recovered from toxicity. The starting dose was 24 g/m²/day. Because our previous trial had shown wide interpatient variability in HMBA pharmacokinetics and excess toxicity at HMBA plasma concentrations greater than 2 mM (HMBA doses between 24 and 33.6 g/m²/day), we attempted to individualize each patient’s dose based on a dosing scheme using an adaptive (feedback) control algorithm, which assumed linear clearance for HMBA. In all courses, a plasma sample was assayed daily and infusion rates were adjusted to achieve an HMBA plasma concentration of 1.5–2.0 mM (300–400 mg/liter). The patients included 12 men and 1 woman with a median age of 56 years (range, 34–76) and median Karnofsky performance status of 90% (range, 60–100). All patients had received prior chemotherapy and 9 patients had also received radiation therapy. The linear adaptive control algorithm was reasonably precise, with a mean absolute error of 0.28 (SE 0.04) mM. However, adjustments in infusion rate systematically overshot the desired change in steady state concentration, probably due to nonlinear clearance of HMBA. For levels within 24 h of a change in infusion rate, this resulted in significant bias, with a mean error of 0.24 (SE 0.09) mM. The mean absolute error was 0.40 (SE 0.06) mM. A second adaptive control algorithm, using a pharmacokinetic model with parallel first-order (renal) clearance and Michaelis-Menten (nonrenal) clearance and using Bayesian parameter estimation with a priori estimates based on our previous phase I trial, proved to be much more precise than the linear model and was unbiased when applied retrospectively to the same observations, with a mean error (within 24 h of a change in infusion rate) of 0.02 (SE 0.06) mM and a mean absolute error of 0.22 (SE 0.03) mM. Toxicity was reversible in all cases and consisted of hallucinations, agitation, somnolence, or confusion, was seen in 2 patients. Four patients complained of insomnia or anxiety. Mild asymptomatic acidosis was seen in 3 patients. Other toxicity included grade 1–2 nausea and vomiting (10 patients), grade 2 diarrhea (2 patients), grade 3 thrombocytopenia (3 patients), grade 1–3 leukopenia (3 patients), and oral herpes simplex infection (4 patients). Mild irreversible renal insufficiency (measured by creatinine clearance) was seen in 8 patients. While no objective responses were seen, 1 patient with non-small cell lung cancer had disappearance of a malignant pleural effusion and a stable endobronchial lesion for 8 months, and 1 patient with recurrent squamous cell carcinoma of the base of the tongue had stable disease for 7 months. The relationship, defined in our previous patient population, between exposure to HMBA and the percentage decrease in platelet count predicted the response in 6 of the current patients well but proved unsuitable in 4 of the current patients. In these 4 patients, the percentage decrease in platelet count was consistently overpredicted. Although the method of adaptive control used in this study proved suboptimal, most patients were managed with mild reversible toxicity, and we believe that refined adaptive control strategies will prove useful for individualized dosing of agents, such as HMBA, which have wide interpatient variability in pharmacokinetics and either excess toxicity above a certain plasma concentration or a narrow therapeutic concentration range.

INTRODUCTION

Because analysis of the structure-activity relationships of a series of bisacetamides indicated it had maximum differentiating activity (1–8), HMBA³ (NSC 95580), a polar-planar compound structurally related to NMF and DMSO, was selected for introduction into clinical trials. HMBA differed from NMF and DMSO, however, in that animal toxicological and pharmacokinetic studies (9) demonstrated the feasibility of achieving plasma HMBA concentrations equal to those required for induction of differentiation in vitro. The induction of morphological and functional differentiation by HMBA in a variety of murine and human leukemic and solid tumor cell lines has been shown to be dependent on both HMBA concentration (2–10 mM) and duration of exposure (at least 12–24 h) (3, 5, 6, 8–11). Lower concentrations of HMBA require longer exposure than do higher concentrations to produce the same differentiation effect in cell lines (6, 8, 9).

Initial phase I studies of HMBA (12, 13), using a 5-day continuous infusion, have shown that $C_{av}$ values of 1–3 mM can be achieved. The maximum tolerable dose of HMBA, given as a 5-day continuous infusion, in these early phase I studies was 33.6 g/m²/day, with 24 g/m²/day being the recommended dose for phase II trials (12, 13). Acute dose-limiting toxicities consisted of a reversible neurotoxicity (obtundation, confusion, hallucinations, and agitation) and reversible anion gap metabolic acidosis. These toxicities were related to the plasma $C_{av}$ of HMBA, in that they rarely occurred at HMBA plasma concentrations of less than 2 mM (12). At plasma concentrations below 2 mM, the duration of infusion was limited by thrombocytopenia (14). Moreover, there is a demonstrable relationship between the HMBA AUC and the percentage change in platelet count from baseline (12).

Due to the aforementioned characteristics of HMBA, it was our desire to dose patients more precisely; therefore we pursued the concept of individualized dosing. Our strategy was based on the fact that in vitro studies have shown that the differentiating activity of HMBA is dependent both on concentration and duration of exposure and on the demonstration in initial phase I trials that (a) $C_{av}$ is achieved in all patients by 12–24 h of infusion, with a subsequent daily variation of 10% or less; (b) a 30% interpatient variability in plasma HMBA $C_{av}$ exists for any given dose; (c) doses of 24–33.6 g/m²/day produce plasma HMBA $C_{av}$ of 1–2 mM; and (d) HMBA $CL_{TB}$ is linearly related to $C_{av}$ and (e) acute dose-limiting toxicity occurs at plasma HMBA $C_{av}$ above 2 mM. Our goal was to achieve and

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³ The abbreviations used are: HMBA, hexamethylene bisacetamide; NMF, N-methylformamide; DMSO, dimethyl sulfoxide; $C_{av}$, steady state plasma concentration; $CL_{TB}$, 24-h creatinine clearance; $CL_{TB}$, total body clearance; AUC, area under the curve of plasma concentration versus time; MAP, maximum a posteriori; $R_0$, infusion rate of HMBA desired, to obtain specified plasma HMBA $C_{av}$; $R_0$, initial HMBA infusion rate; ME, mean absolute error; ME, mean error.
maintain a desired plasma HMBA \( C_m \) of 1.5–2.0 mM. An adaptive (feedback) control algorithm, which assumed "locally" linear clearance of HMBA, was used prospectively to individualize each patient's HMBA exposure to 1.5–2.0 mM for 5 days. Additional goals were to document toxicity or tumor regression seen at this plasma HMBA \( C_m \) and duration of exposure and to refine the pharmacokinetic-pharmacodynamic interrelationships of HMBA.

**MATERIALS AND METHODS**

**Patient Selection and Evaluation.** All patients entered in this study had histological proof of a malignancy for which conventional therapy had proven ineffective or for which no other therapy with established efficacy was available. All patients had a minimum life expectancy of 12 weeks and a Karnofsky performance status of at least 60% and had not received chemotherapy or radiation therapy within 4 weeks of entry into the study (8 weeks for agents with delayed hematological toxicity such as mitomycin C or nitrosoureas). All patients had adequate bone marrow function (WBC at least 3,500/µl and platelet count at least 100,000/µl), adequate liver function (bilirubin less than 2.0 mg/dl), and adequate renal function (serum creatinine less than 2.0 mg/dl or measured 24-h \( C_m \) at least 60 ml/min/1.73 m²). Patients were excluded from the study if they had a seizure disorder, central nervous system malignancy, or history of major psychiatric illness. Studies obtained prior to HMBA administration included hematocrit, WBC with differential, platelet count, urinalysis, and determination of serum urea nitrogen, creatinine, glucose, alkaline phosphatase, total bilirubin, aspartate aminotransferase, alanine aminotransferase, calcium, and phosphorus. All patients had an initial chest radiograph and electrocardiogram. Eight patients had a baseline 24-h \( C_m \) measured. Patients in the study had weekly assessments that included physical examination, determination of weight and performance status, and complete blood count. All other laboratory work was obtained at least every 4 weeks. Measurable disease was not required but was measured serially when present. Prior to receiving HMBA, each patient had the investigational nature of the treatment explained, and an informed consent, approved by the University of Maryland Institutional Review Board, was signed. Toxicity criteria were those of the National Cancer Institute, Division of Cancer Treatment. Response criteria included complete response (disappearance of all evidence of malignant disease for at least 4 weeks), partial response (reduction by at least one-half in the sum of the products of all measurable lesions or appearance of new lesions for at least 4 weeks), and progression of disease (increase by at least 25% in the sum of the products of all evidence of malignant disease for at least 4 weeks), partial response (reduction by at least one-half in the sum of the products of all measurable lesions or appearance of new lesions for at least 4 weeks), and progression of disease (increase by at least 25% in the sum of the products of all measurable lesions or appearance of new lesions for at least 4 weeks).

**Drug Schedule and Administration.** HMBA was supplied by the Investigational Drug Branch of the National Cancer Institute (Bethesda, MD). Each 500-ml bottle contained 15, 25, or 50 g of HMBA as a solution in 0.154 M NaCl or 5% dextrose in water. HMBA was administered by continuous infusion through a free-flowing peripheral or central venous catheter. The rate of HMBA infusion was controlled by a Travenol Flo-Gard 8000 volumetric infusion pump (Travenol Laboratories, Inc., Deerfield, IL).

Because our previous phase I trial (12) demonstrated no acute dose-limiting toxicity (neurotoxicity or metabolic acidosis) associated with a dose of 24 g/m²/day for 5 days, and because that dose produced no plasma HMBA \( C_m \) greater than 2 mM, patients in the current trial received an initial HMBA infusion of 24 g/m²/day. The infusion rate was adjusted daily to maintain plasma HMBA concentrations of 1.5–2.0 mM (300–400 mg/liter), according to the adaptive control algorithm described below.

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**Adaptive Control Algorithm.** The objective of the adaptive control algorithm was to achieve and maintain an HMBA \( C_m \) between 1.5 and 2.0 mM. After 16 to 24 h of \( R_0 \), the infusion rates were calculated as follows:

\[
R_s = \frac{R_0 \times C_m\text{(observed)}}{C_m\text{(desired)}}
\]

where \( R_0 \) represented the initial, or current, infusion rate. The assumptions underlying this approach were that by 16–24 h steady state had been achieved and that a change in infusion rate would result in a proportional change in \( C_m \) (i.e., that HMBA clearance was "locally" linear). All courses were controlled by this algorithm.

We retrospectively applied a more complex method, which employed a model with parallel first-order (renal) clearance and Michaelis-Menten nonrenal clearance, to 19 courses in 10 patients. HMBA plasma concentrations were predicted (based on the patient's body surface area, all values of \( C_m \), and previous HMBA doses and plasma concentrations) using a Bayesian parameter estimation with \( a \) priori estimates based on our previous phase I trial (12, 16). With this method, a computer is required to calculate each patient's own parameter (\( V_{\text{max}}, K_m, \) slope values and the new infusion rate (\( R_s \)) calculated as:

\[
R_s \text{ (mg/1.73 m²/h) } = \frac{V_{\text{max}}}{K_m + C_m + \text{slope} (C_m)} \times C_m
\]

where \( C_m \) is the desired steady state HMBA plasma concentration in mg/liter, \( V_m \) is the slope relating the renal clearance of HMBA to \( C_m \), \( V_m \) is the maximum nonrenal HMBA elimination rate, and \( K_m \) is the concentration of HMBA at which the nonrenal elimination rate of HMBA is half of \( V_{\text{max}} \). The development and prospective validation of this second approach are in progress (16-19).

**RESULTS**

**Patient Population.** Thirteen patients received 30 courses of HMBA, all of whom were evaluable for toxicity; 11 patients were evaluable for response (Table 1). There were 12 men and 1 woman, with a median age of 56 years (range, 34–76 years) and a median Karnofsky performance status of 90% (range, 60–100%). All patients had received prior chemotherapy, and 9 patients had also received radiation therapy. Six patients were receiving concomitant narcotic analgesics. Seven patients received 1 course of HMBA, 4 patients received 2 courses, and 1 patient each received 7 and 8 courses.

**Nonhematological Toxicity.** Nonhematological toxicity (Table 2) was reversible in all patients. Neurotoxicity was seen in 6 patients. This was manifested as mild confusion in 1 patient, anxiety in 2 patients, insomnia in 2 patients, and visual hallucinations in 1 patient. Five of these 6 patients were receiving concomitant narcotic analgesics. Anxiety and insomnia

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>No. of patients</th>
<th>No. evaluable for response†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Unknown small cell lung carcinoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Head/neck</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Multiple (non-small cell lung and prostate)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Criteria for evaluation included measurable disease and at least one course of treatment.

Plasma HMBA concentrations were assessed with our modification of the gas chromatographic method of Kelley et al. (15). The quantitative aspects of this method in our laboratory have been published previously (12).

The rate of HMBA infusion was 24 g/m²/day. The infusion rate was adjusted daily to maintain plasma HMBA concentrations of 1.5–2.0 mM (300–400 mg/liter), according to the adaptive control algorithm described below.

Treatment was repeated every 28 days, if the patient had recovered from drug toxicity and had at least stable disease.

The rate of HMBA infusion was 24 g/m²/day. The infusion rate was adjusted daily to maintain plasma HMBA concentrations of 1.5–2.0 mM (300–400 mg/liter), according to the adaptive control algorithm described below.

Treatment was repeated every 28 days, if the patient had recovered from drug toxicity and had at least stable disease.
Table 2: Nonhematological toxicity encountered with adaptive control for target HMBA \( C_m \) of 1.3–2.0 mM

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade (NCI)</th>
<th>No. of patients/no. of courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>1</td>
<td>1/1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>2/2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>2/3</td>
</tr>
<tr>
<td>Hallucination</td>
<td>4*</td>
<td>1/1</td>
</tr>
<tr>
<td>Acidity, serum bicarbonate (meq/liter)</td>
<td>19</td>
<td>N/A*</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>N/A*</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>N/A*</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>3/3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1/1</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2</td>
<td>7/9</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4/5</td>
</tr>
<tr>
<td>Hematoma</td>
<td>2</td>
<td>1/1</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2</td>
<td>1/1</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>2</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1/1</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>2</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3/4</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>N/A*</td>
<td>1/1</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>3</td>
<td>1/1</td>
</tr>
<tr>
<td>Oral herpes simplex</td>
<td>1–2</td>
<td>4/4</td>
</tr>
</tbody>
</table>

* NCI, National Cancer Institute; N/A, not applicable because grading criteria do not exist.
* HMBA \( C_m \) = 2.9 mM.

seemed to be consistent from course to course, but the confusion seen in 1 patient only occurred in 1 (course 6) of 8 courses. The patient who experienced hallucinations had a plasma HMBA concentration of 2.9 mM. The hallucinations resolved when the infusion rate was decreased so that the plasma HMBA concentration was reduced to 1.6 mM.

Mild asymptomatic acidosis was observed. The decrease in serum bicarbonate generally resolved within 24 h after cessation of HMBA infusion. Nadir serum bicarbonate was 17–19 meq/liter in 3 patients (5 courses). Grade 1–2 nausea and vomiting were nearly universal, occurring in 10 patients (14 courses). Antiemetics controlled these symptoms adequately for the majority of patients. Grade 1–2 diarrhea was occasionally observed. Three patients had mild transient elevations of bilirubin, lactate dehydrogenase, or alkaline phosphatase. However, these patients had carcinoma metastatic to the liver and, in each case, the elevated liver function tests were associated with progression of their underlying malignancy. Oral herpes simplex was seen in 4 patients. In 1 patient, this syndrome recurred with his second course of HMBA. Mild renal toxicity was observed. The median increase of serum urea nitrogen over baseline was 20% (range, –2 to 121%), and the median increase of serum creatinine over baseline was 32% (range, 8 to 110%). Although only grade 1–2 increases in serum creatinine were observed, the consistent increases over baseline in the initial 5 patients led us to obtain serial 24-h HMBA concentrations in subsequent patients. In 8 patients, the median decrease in \( C_m \) from baseline was 24% (range, –36 to 48%). The maximum decrease in renal function was generally observed by day 2 or 3 and remained at the same level throughout the HMBA infusion. Renal function returned to baseline in all patients prior to the next course of HMBA.

Other toxicities included mild fluid overload in 1 patient who received HMBA in 0.154 M NaCl, hematemesis (without thrombocytopenia) in 1 patient with rapid disease progression, mucositis in 1 patient, and headache in 1 patient. One patient experienced chills and fever related to an intraabdominal abscess (without leukopenia).

Hematological Toxicity. No anemia was attributable to HMBA. Grade 3 thrombocytopenia was seen in 2 patients (3 courses). The median percentage change in platelet count, i.e.,

\[
\frac{\text{Pretreatment platelet count} - \text{nadir platelet count}}{\text{Pretreatment platelet count}} \times 100
\]

was 41% (range, 10–84%) for 28 courses. There was no evidence of cumulative platelet toxicity. Grade 2–3 leukopenia was seen in 1 patient, who had been treated previously for sarcoma and whose baseline WBC was 3500/µl. Grade 1 leukopenia was seen in 2 patients.

Bias and Precision of the Adaptive Control Algorithm. Fifty-five of 73 total plasma HMBA concentrations were prospectively predicted according to the “linear” adaptive control algorithm. The first plasma HMBA concentrations of each course were excluded. Linear regression of observed (\( O \)) versus predicted (\( Pr \)) concentrations resulted in a line of best fit of: \( O \) (mM) = 1.2 \times Pr (mM) – 0.16 mM \( r = 0.82 \). This line was not different from the line of identity (0.05 < \( P < 0.10 \)).

The ME was computed as a measure of bias: \( ME = \frac{\sum (O - Pr)}{N} \), where \( N \) is the total number of observations. The ME for all 55 data points was 0.18 (SE 0.05) mM. This is not significantly different from zero (0.05 < \( P < 0.10 \)), the approach is, overall, unbiased. However, when infusion rates were adjusted as above, significantly larger than proportional changes in HMBA \( C_m \) were systematically achieved. That is, an increase in the infusion rate resulted in a \( C_m \) greater than desired and a decrease in rate provided plasma HMBA concentrations lower than desired. Many of the 55 predictions were from periods in which the infusion rates were unchanged for 48 h or more. The bias of the algorithm is reflected better by the 22 predictions that were made within 24 h of a change in infusion rate. The ME for this subset of data was 0.24 (SE 0.09) mM. This demonstrates significant bias (\( P < 0.001 \)).

The MAE was computed as a measure of precision:

\[
\text{MAE} = \frac{\sum |O - Pr|}{N}
\]

The MAE for all 55 points was 0.28 (SE 0.04) mM. The MAE for the 22 observations within 24 h of a change in infusion rate was 0.40 (SE 0.06) mM.

We retrospectively applied a second method, with a more complex pharmacokinetic model, to the same 55 HMBA plasma determinations described above (16). This MAP Bayesian approach was more precise and was unbiased: \( O \) (mM) = 0.998 \times Pr (mM) – 0.038 mM \( r = 0.893 \); line not different from the line of identity, \( P < 0.05 \). The ME was 0.03 (SE 0.04), and the MAE was 0.22 (SE 0.03) mM. Within 24 h of a change in infusion rate, the MAP Bayesian method was much less biased, with ME of –0.02 (SE 0.06) mM, and was much more precise, with MAE of 0.22 (SE 0.03) mM, than was the linear algorithm.

Pharmacokinetic/Pharmacodynamic Relationships. Our previous trial of HMBA (12) defined a relationship between the percentage change in platelet count and the HMBA AUC. This relationship was adequately described by two equations. In the current study, we evaluated whether our modification (12) of the Hill equation (20)

\[
\% \text{ decrease in platelets} = \frac{100}{(1033)^{1.25} + (\text{AUC})^{1.25}}
\]
adequately described the percentage change in platelet count seen in this trial. In this model, percentage decrease in platelet count is the measured effect, 100 represents the maximum possible effect, 1033 is the fitted AUC that gives 50% of the maximum effect, and 1.55 is a fitted Hill constant. When the change in platelet count observed in 19 courses in 10 patients was compared to that which would have been predicted by the above equation, the relationship was significantly different from the line of identity, with an $r^2$ of 0.464. The relationship overpredicted the drop in platelet count, with a ME of $-95.6 \times 10^3$ (SE 86.5 $\times 10^3$) and MAE of $101.9 \times 10^3$ (SE 78.5 $\times 10^3$). Essentially the same results were obtained when the data from the current trial were fitted to the other equation which adequately described the relationship of the percentage decrease in platelet count and the HMBA AUC in our previous trial

\[
% \text{ decrease in platelet count} = 100 \left(1 - e^{-0.000652 \text{ AUC}}\right).
\]

Further examination of these results revealed that the responses of 6 patients were well predicted. Of the 4 patients whose responses were poorly predicted, all were much less sensitive than predicted to the thrombocytopenic effect of HMBA. Three of these 4 patients had repeat courses of HMBA and the subsequent pharmacodynamic responses to HMBA were very consistent within each patient. In response to these findings, we developed (18) a MAP Bayesian computer program which can estimate an individual's pharmacodynamic parameter values after at least 1 course has been observed. The \textit{a priori} estimates of AUC$_{50}$ and the Hill constant were based on our previous phase I population. Retrospective application of this program, using the modified Hill equation, to the 19 courses described above yielded predictions of the percentage change in platelet count with a ME of $-47 \times 10^3$ (SE 23.4 $\times 10^3$) and MAE of $75.1 \times 10^3$ (SE 18.9 $\times 10^3$).

Responses. There were no objective tumor responses. However, a patient with a non-small cell lung cancer and malignant pleural effusion had disappearance of the effusion (without thoracentesis) as measured by chest X-ray, after 3 courses of HMBA. He also had disappearance of a lesion visible on endobronchoscopic examination, but cytology was persistently positive for malignancy. This patient received a total of 8 courses without progression of the lung cancer. However, when his previously treated large cell lymphoma relapsed after the 8th course of HMBA, he was treated with local radiation and HMBA therapy was discontinued. An additional patient was treated with HMBA for 7 months, during which time there was no growth of a recurrent carcinoma at the base of the tongue. He progressed after course 7, and HMBA therapy was discontinued.

**DISCUSSION**

HMBA differs from other differentiating agents such as DMSO and NMF, which have previously undergone clinical trials (1, 2, 21-26), in that animal toxicological and pharmacological studies (27) suggested that the plasma HMBA concentrations achievable in patients would be equivalent to those which caused differentiation \textit{in vitro}. However, our initial phase I trial of this agent showed wide interindividual but narrow intrapatient variation in pharmacokinetics (12). Because HMBA-associated differentiation is both time and concentration dependent \textit{in vitro} and because neurotoxicity and metabolic acidosis are seen at plasma HMBA concentrations above 2 mM, we prospectively used an adaptive control algorithm to maintain each patient's HMBA $C_s$ in the desired range of 1.5-2.0 mM (300-400 mg/liter). The linear controller used was based on two main assumptions: (a) that $C_m$ was achieved within 16-24 h of constant-rate infusion; and (b) that a change in infusion rate would result in a proportional change in $C_m$ (i.e., the HMBA $CL_{TB}$ was locally linear in the range of concentrations being considered). The second of these assumptions is apparently incorrect and much of the loss in precision of control of HMBA $C_m$ was probably due to nonlinearity in HMBA $CL_{TB}$. This linear algorithm, if valid, would have been attractive because it is computationally very simple. On the basis of the results presented in this paper, we have developed (16) and are prospectively validating a more rigorous adaptive control algorithm (18). It uses a more complex pharmacokinetic model and requires a computer to calculate changes in infusion rate based on daily HMBA plasma concentrations. We will use this controller for future patients receiving HMBA.

It appears that there is also modest intrapatient but considerable interindividual variability in the pharmacodynamics of HMBA, at least with regard to change in platelet count. When HMBA $C_m$ is controlled in the range of 1.5-2.0 mM, acute dose-limiting toxicities are not seen. Since response \textit{in vitro} depends both on concentration and on duration of exposure, a longer duration of HMBA infusion should lead to greater activity. However, the duration of infusion will likely be limited by thrombocytopenia (14). Our present data indicate that individual patients will show fairly wide differences in the amount of thrombocytopenia produced by a given AUC and will likely tolerate significantly different maximum durations of HMBA infusions at $C_m$ 1.5-2.0 mM.

Our retrospective attempt to predict platelet changes after the initial course, using estimates of the patient's own pharmacodynamic parameter values, was very encouraging. It suggests that HMBA plasma concentrations could be controlled to achieve maximally tolerable $C_m$ and that, after the first course, the pharmacodynamic parameter values could be estimated and used to predict prospectively the maximally tolerable duration of infusion for individual patients.

Other toxicities seen in this trial are consistent with those reported previously (12-14). Of interest is the lack of severe acidosis when plasma HMBA concentrations are maintained at less than 2.0 mM. Neurotoxicity was also mild, except for one instance of visual hallucinations experienced by a patient with a plasma HMBA concentration of 2.9 mM. This HMBA concentration was much higher than our target range and in our previous phase I trial was associated with a greater likelihood of neurotoxicity (12). Most of the patients who experienced neurotoxicity were also receiving other centrally active drugs, notably narcotic analgesics, and the potential role of these drugs in the predisposition for neurotoxicity from HMBA remains undefined.

Although no objective responses were seen, the disappearance of a pleural effusion in a patient with non-small cell lung cancer and the lack of progression of disease in a patient with relapsed squamous carcinoma of the head and neck are encouraging results. It may be that traditional measures of drug efficacy, such as tumor shrinkage, do not apply to a differentiating agent or that we have not yet achieved optimal concentration of, or duration of exposure to, this drug.

Adaptive control represents a very promising approach to the optimization of regimens with drugs, such as HMBA, which have: (a) specific target plasma concentrations; (b) only a small difference between desired and toxic plasma concentrations; and (c) wide and poorly predictable intersubject variability in pharmacokinetics and pharmacodynamics. The results pre-
Presented in this paper constitute an initial attempt at applying this concept to oncological chemotherapy. Ongoing studies at our center are focused on refinement of the pharmacokinetic and pharmacodynamic models, on prospective validation of these techniques, and on development of methods for circumventing some of the acute toxicities associated with high HMBA Cums in hopes of duplicating the conditions which cause optimal differentiation in vitro.

REFERENCES

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