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

Barbara A. Conley,² Alan Forrest, Merrill J. Egorin, Eleanor G. Zuhowski, Victoria Sinibaldi, and David A. Van Echo

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 $C_m$ 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 $C_m$ 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 on duration of exposure and on the demonstration in initial phase I trials that (a) $C_m$ 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 $C_m$ exists for any given dose; (c) doses of 24–33.6 g/m²/day produce plasma HMBA $C_m$ of 1–2 mM; (d) HMBA $C_L$ is linearly related to $C_m$ and; (e) acute dose-limiting toxicity occurs at plasma HMBA $C_m$ above 2 mM. Our goal was to achieve and maintain plasma HMBA concentrations to the extent possible.

³The abbreviations used are: HMBA, hexamethylene bisacetamide; NMF, N-methylformamide; DMSO, dimethyl sulfoxide; $C_m$, steady state plasma concentration; $C_L$, 24-h creatinine clearance; $C_L$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 $C_m$; $R_0$, initial HMBA infusion rate; MAE, mean absolute error; ME, mean error.

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maintain a desired plasma HMB A \( C_m \) of 1.5–2.0 mM. An adaptive (feedback) control algorithm, which assumed "locally" linear clearance of HMB A, was used prospectively to individualize each patient's HMB A exposure to 1.5–2.0 mM for 5 days. Additional goals were to document toxicity or tumor regression seen at this plasma HMB A \( C_m \) and duration of exposure and to refine the pharmacokinetic-pharmacodynamic interrelationships of HMB A.

**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 HMB A 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 HMB A, 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 and no 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 within 4 weeks).

**Drug Schedule and Administration.** HMB A 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 HMB A as a solution in either 0.154 M NaCl or 5% dextrose in water. HMB A was administered by continuous infusion through a free-flowing peripheral or central venous catheter. The rate of HMB A 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 HMB A \( C_m \) greater than 2 mM, patients in the current trial received an initial HMB A infusion of 24 g/m²/day. The infusion rate was adjusted daily to maintain plasma HMB A 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.

**Analysis of Plasma HMB A Concentration.** Heparinized blood samples were obtained before and at approximately 24-h intervals during the HMB A infusion. Blood samples were immediately centrifuged at 1000 \( \times \) g for 10 min, and the resulting plasma supernatants were immediately removed and analyzed.

Plasma HMB A 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).

**Adaptive Control Algorithm.** The objective of the adaptive control algorithm was to achieve and maintain an HMB A \( C_m \) between 1.5 and 2.0 mM. After 16 to 24 h of \( R_0 \) of 24 g/m²/day, and every 24 h during the course, a plasma HMB A concentration was obtained as above. The \( R_0 \) was calculated with the equation

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

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 proportionate change in \( C_m \) (i.e., that HMB A 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. HMB A plasma concentrations were predicted (based on the patient's body surface area, all values of \( C_m \), and previous HMB A doses and plasma concentrations) using 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 (\( V_{max} \), \( K_m \), slope) values and the new infusion rate (\( R_0 \)) is calculated as follows:

\[
R_0 \text{ (mg/1.73 m²/h)} = \frac{V_{max}}{K_m + C_m} + \text{slope} (C_m) \cdot C_m
\]

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

**RESULTS**

**Patient Population.** Thirteen patients received 30 courses of HMB A, 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 HMB A, 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>Table 1 Distribution of 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 (non-small cell lung carcinoma)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Unknown primary</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>
<tr>
<td>Sarcoma</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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

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We prospectively used an adaptive control algorithm to maintain each patient's HMBA Css in the desired range of 1.5-2.0 mM. The linear controller used was based on two main assumptions: (a) that Cm 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 Cm (i.e., the HMBA CLTB 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 Cm was probably due to nonlinearity in HMBA CLTB. 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 intraindividual but considerable interindividual variability in the pharmacodynamics of HMBA, at least with regard to change in platelet count. When HMBA Cm is controlled in the range of 1.5-2.0 mM, acute dose-limiting toxicities are not seen. Since response 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 Cm 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 Cm 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.

**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 in vitro. However, our initial phase I trial of this agent showed wide interindividual but narrow intraindividual variation in pharmacokinetics (12). Because HMBA-associated differentiation is both time and concentration dependent 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 Cm in the desired range of 1.5-2.0 mM (300-400 mg/liter). The linear controller used was based on the equation:

\[
\% \text{ decrease in platelet count} = 100 \left(1 - e^{-0.000052 \text{ AUC}}\right).
\]

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 *a priori* estimates of AUC50 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 x 10³ (SE 23.4 x 10³) and MAE of 75.1 x 10³ (SE 18.9 x 10³).

**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 HMBA therapy was discontinued, an additional patient was treated with local radiation and the HMBA AUC in our previous trial

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sented 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 $C_{\text{ss}}$, in hopes of duplicating the conditions which cause optimal differentiation in vitro.

REFERENCES

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