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# Phase I Study of Ethylbis(2,2-dimethyl-1-aziridinyl)phosphinate (AB-163)*

G. L. Wampler, M. Kuperminc, and W. Regelson

Division of Medical Oncology, Department of Medicine, Medical College of Virginia, Richmond, Virginia 23298, USA

***Summary.*** *Ethylbis(2,2-dimethyl-1-aziridinyl)phosphinate (AB-163) was used to treat 27 patients in a phase I trial. The limiting toxicity on a weekly schedule of IV administration involved nausea and vomiting associated with a variety of cholinergic side effects, including possible seizures. A starting dose of 300–400 mg/M²/week is suggested for a Phase II trial. One partial response in a patient with squamous-cell carcinoma of the cervix metastatic to the lungs was seen.*

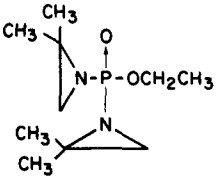


**Fig. 1.** Structural formula for AB-163

## Introduction

Radiation potentiation was noted both in mouse models [8] and in clinical trials [5] with the use of ethylbis(2,2-dimethyl-1-aziridinyl)phospinyl carbamate (AB-132). This drug is one of a series of 'dual antagonists', a term introduced by Bardos et al. [3, 4] to describe certain chemotherapeutic agents incorporating the biologically essential features of two different but synergistic inhibitors into a single molecule. A new member of this series, ethylbis(2,2-dimethyl-1-aziridinyl) phosphinate (AB-163) (Fig. 1), proved to be much more effective than AB-132 in the treatment of a spectrum of transplanted animal tumors [7]. AB-163 has been tested for radiation-potentiating effects in a P388 murine leukemia model first utilized by Wodinsky et al. [11], in which it was found to be synergistic (or supra-additive) in its effect [10]. The radiation-potentiating effects of certain members of this series of compounds have been attributed, on theoretical grounds, to the methylated aziridine rings in the structure [2].

AB-163, which has both alkylating and phosphorylating activities [2], has been compared with a series of both standard and new alkylating agents against a cyclophosphamide-resistant strain of L1210 leukemia. In this study AB-163 was one of the best agents and was superior in activity to tris(aziridinyl)phosphine sulfide (thio-TEPA), the nearest analog in clinical use. In this cyclophosphamide-resistant system no cross-resistance to the dual antagonists was demonstrated [9].

Acute toxicity studies in ICR/Ha male mice showed that AB-163 was more toxic by the IP than by the IV route, the $LD_{50}$ values being 159 and 198 mg/kg, respectively. In Beagle dogs a dose of 2 mg/kg/day resulted in loss of appetite during the 4th week of treatment, a dose of 8 mg/kg/day resulted in fatality in one animal out of two (Day 18 of pneumonia), and 20 mg/kg/day resulted in the deaths of both animals receiving this dose on Day 9 from bone marrow depression. Doses of 8 mg/kg/day produced intensive vomiting, foaming at the mouth, increased salivation, and CNS stimulation with convulsions [7].

## Materials and Methods

AB-163, originally synthesized by Chmielewicz et al. [6], was supplied in 200 mg vials by Starks Associates, Buffalo, New York. The drug was stored at −20° C until use, and was administered weekly by rapid IV drip in saline over 10–15 min in successively increasing dosages to groups of cancer patients, starting at 40 mg/M², for a minimum of 4 weeks or until dose-limiting toxicity was observed. A total of 27 patients were treated. Patients were monitored, with medical history and physical examination, blood counts, serum chemistries, and weight

* Formerly ethylbis-(2,2-dimethyl)-ethylenamido phosphate (NSC 108878)

*Reprint requests should be addressed to:* G. L. Wampler at Box 292, MCV Station, Richmond, Virginia 23298, USA

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**Table 1.** Characteristics of the patients included in the phase I study of AB-163

| | | |
|---|---|---|
| Types of malignancies | | |
| Squamous-cell carcinomas (16) | Cervix (8)<br>Lung (2)<br>Esophagus (2)<br>Soft palate (1)<br>Pyriform sinus (1)<br>Vagina (1)<br>Penis (1) | |
| Adenocarcinomas (7) | Colon (2)<br>Breast (2)<br>Ovary (1)<br>Uterus (1)<br>Lung (1) | |
| Melanomas (1) | | |
| Sarcomas (2) | Chondrosarcoma (1)<br>Leiomyosarcoma (1) | |
| Lymphoepithelioma (1) | Soft palate (1) | |
| Sex: | 11 males | 16 females |
| Race: | 22 whites | 5 blacks |
| Age at diagnosis | Median 55 | Range 27–74 |
| Age on study | Median 56 | Range 28–76 |
| Months from diagnosis to study | Median 18 | Range 1–324 |

changes. No concurrent cytotoxic drug therapy was permitted and other drug therapy was generally kept constant throughout protocol treatment. An exception to this was the use of antiemetics, which were frequently required during treatment; prochlorperazine, haloperidol, or benzquinamide hydrochlorides was usually used. In addition, diphenoxylate hydrochloride was used in several instances to control diarrhea.

Patients included in this study all had malignant disease. Most had been previously treated with chemotherapy but had normal or near-normal hematologic values and serum chemistries. Patient characteristics are outlined in Table 1.

## Results

Patients receiving less than 100 mg/M$^2$/week had no side effects. With between 100 and 200 mg/M$^2$/week nausea and vomiting were seen in at least 50% of the patients. Side effects were generally not dose-limiting, but one patient refused to continue treatment at a dose of 200 mg/M$^2$/week because of nausea and vomiting, and the other one required a dose reduction. With between 200 and 300 mg/M$^2$/week more severe nausea and vomiting were encountered, with accompanying diarrhea, loss of appetite, weight loss and, in some patients, central nervous system toxicity. Neurotoxicity was more common at doses above 300 mg/M$^2$/week and consisted of disturbance of sleep patterns, inability to sleep, dreams, hallucinations, weakness, and tremulousness. In two patients receiving doses above 400 mg/M$^2$/week possible convulsive episodes occurred. Two patients complained of increased secretions in the throat. At doses above 500 mg/M$^2$/week abdominal pain associated with severe nausea and vomiting was seen in two patients. The highest dose of AB-163 that could be sustained for several weeks was approximately 400 mg/M$^2$/week. Four patients receiving 500 mg/M$^2$ or more required dose reduction in the second week, while one patient received two doses of 500 mg/M$^2$ (Table 2).

While neurologic side effects were commonly elicited, nausea and vomiting were the most frequent dose-limiting toxic effects. Nausea typically began several hours after the treatment and lasted several hours to 2 days, depending on the dose. In some cases it persisted throughout the week. Nausea and vomiting were associated with complaints of weakness or a general malaise that was not well described by patients but resulted in several of them seeking help from other physicians or in emergency rooms 1 or 2 days after administration of AB-163. Diarrhea, when it occurred, tended to come on after several injections and was relatively easy to control.

Two cases of possible seizures are described: (1) A 55-year-old white female with carcinoma of the cervix with peritoneal and omental implants was brought to the emergency room shortly after receiving her third dose of 400 mg AB-163/M$^2$. She was reported to have passed out with left-sided weakness; however, examination in the emergency room showed no neurologic deficit. She was admitted to rule out brain metastases. An electroencephalogram and a brain scan were normal. No further AB-163 was given. (2) A 28-year-old black female with squamous-cell carcinoma of the vagina metastatic to the retroperitoneal area with ureteral obstruction lost consciousness on her way to the clinic when she was scheduled to receive her seventh dose of 400 mg AB-163/M$^2$. A questionable seizure occurred, and the patient was comatose when seen in the clinic. The patient was admitted and had a metastatic central nervous system work-up, which was negative. The incident was attributed to high doses of levorphanol, which was being taken for pain relief. She then received her seventh dose of AB-163 without further difficulty, but there had been a 3-week lapse, i.e., two missed doses, during that interval.

No disturbance of kidney or liver function was detected in any patient.

Patient no. 14 (Table 2) received 2,400 mg/M$^2$ over 8 weeks, patient no. 22 received 2,900 mg/M$^2$ over 10 weeks, and patient no. 21 received 5,200 mg/M$^2$ over 16 weeks. Of the patients in this study, these three patients received the highest cumulative doses of AB-163.

One partial response was seen, in patient no. 21, who had carcinoma of the cervix metastatic to the lungs, liver, and bone. The lung nodules regressed by 50% cross-sectional area. Maximum regression was at 8 weeks, while the duration of response was 7 weeks.

**Table 2.** Individual patient toxicity of AB-163

| Pt. no. | Dose ($mg/M^2$)[a] | WBC $mm^3/10^3$ Start/Nadir[b] | Plts. $mm^3/10^3$ Start/Nadir[b] | Nausea vomiting[c] | Diarrhea[c] | Weight loss[d] | Other side effects | Limiting toxicity |
|---|---|---|---|---|---|---|---|---|
| 1 | 40 × 4 | 10.9/7.9 | 308/215 | 0 | 0 | Gain | 0 | 0 |
| 2 | 40 × 4 | 19.6/19.0 | 532/180 | 0 | 0 | −8%[e] | 0 | 0 |
| 3 | 80 × 4 | 7.7/5.25 | 200/172 | 0 | 0 | −2% | 0 | 0 |
| 4 | 80 × 4 | 10.0/8.4 | 208/154 | 0[f] | 2[g] | Gain | 0 | 0 |
| 5 | 120 × 2[h] | 14.0/13.4 | 396/258 | 2 | 0 | ID[i] | Felt ill, weakness | 0 |
| 6 | 120 × 5 | 8.4/7.4 | 624/535 | 0 | 0 | −8% | 0 | 0 |
| 7 | 150 × 4 | 17.8/17.0 | 351/300 | 0 | 0 | ID[i] | 0 | 0 |
| 8 | 150 × 1[j] | 10.1/10.1 | 524/334 | 2 | 0 | −1% | 0 | 0 |
| 9 | 200 × 5 | 3.5/3.5 | 177/177 | 0 | 0 | −6% | Anorexia | 0 |
| 10 | 200 × 2[k] | 4.3/5.2 | 221/211 | 3 | 0 | −3% | 0 | GI |
| 11 | 250 × 2[l] | 4.4/3.5 | 228/176 | 3 | 0 | ID[i] | Anginal pains post treatment | GI |
| 12 | 250 × 7 | 4.1/3.3 | 303/189 | 0 | 0 | −1% | Dizziness | 0 |
| 13 | 300 × 6 | 7.7/7.1 | 163/163 | 0 | 2 | −13% | Anorexia, bad dreams | 0 |
| 14 | 300 × 8 | 6.1/4.2 | 314/140 | 0 | 0 | Gain | 0 | 0 |
| 15 | 300 × 4 | 16.8/10.1 | 287/264 | 3 | 2 | −3% | Anorexia | 0 |
| 16 | 350 × 3[m] | 5.3/4.6 | 389/320 | 0 | 0 | −7% | Dreams, visual hallucinations | 0 |
| 17 | 350 × 2 | 6.6/6.5 | 310/303 | 3 | 0 | Gain | 0 | GI |
| 18 | 350 × 2 | 5.0/3.7 | 301/175 | 2 | 0 | −5% | 0 | 0[n] |
| 19 | 400 × 3 | 10.1/7.8 | 268/268 | 2 | 2 | −5% | 0 | CNS[o] |
| 20 | 400 × 2[p] | 5.0/3.9 | 247/247 | 2 | 0 | ID[i] | Tachycardia, weakness, trembling, increased mucous secretion in throat | 0[p] |
| 21 | 400 × 13[q] | 10.4/6.1 | 205/156 | 0 | 0 | −10% | 0 | 0 |
| 22 | 400 × 7 | 6.7/6.7 | 330/256 | 2 | 0 | −9% | Insomnia, weakness, anorexia | CNS[o] |
| 23 | 500 × 1 | 9.1/8.3 | 267/259 | 3 | 0 | Gain | 0 | GI |
| 24 | 500 × 1 | 6.2/5.8 | 201/128 | 3 | 0 | −6% | Abdominal pains, dreams, burning in feet | GI |
| 25 | 500 × 2 | 9.0/9.0 | 531/217 | 3 | 0 | −4% | Abdominal cramps | GI |
| 26 | 600 × 1 | 6.5/6.3 | 200/200 | 3 | 0 | 0 | 0 | GI |
| 27 | 600 × 1 | 10.7/9.3 | 458/247 | 3 | 0 | −3% | Secretions at night | GI |

[a] Patients were treated weekly by intravenous drip. After receiving the number of treatments indicated, some patients continued to receive drug at a lower dose. Some patients at lower doses without side effects had escalation of dose after 4 weeks
[b] Lowest recorded lab values during course of treatment and for 3 weeks thereafter where information available
[c] Maximum zubrod toxicity Score: 1 = mild, 2 = moderate, 3 = severe
[d] Maximum weight loss (percent of initial body weight) during treatment at this dose and for one week following last treatment
[e] Diuresis resulted in weight loss
[f] Increase in dose to 100 $mg/M^2$ produced nausea and vomiting
[g] Diarrhea attributed to disease, not treatment
[h] Only 2 doses because supply of drug was interrupted
[i] Insufficient data
[j] Continued treatment at 100 $mg/M^2/wk$ × 8. Mild nausea persisted
[k] Refused further treatment because of nausea and vomiting
[l] Continued treatment at 125 $mg/M^2/wk$ × 10
[m] Patient taken off before 4 doses because of general deterioration thought to be on the basis of progressive disease
[n] Third dose reduced but no clear limiting toxicity noted on review
[o] Possible convulsion (see text)
[p] Patient died after 2 treatments
[q] Three skipped doses due to intermittent infections or other complications

## Discussion

The results differ from the dog data [7], in that marrow toxicity secondary to the administration of AB-163 was not seen in man. The point of occurrence of the occasional low white blood cell counts seen varied with respect to the time of administration of the drug in the individual patient, and no dose/marrow toxicity relationship was evident in the study group (see Table 2). Possible explanations for this difference include species difference in toxic mani-

festations, the use of a different schedule of drug administration in man, and the use of higher doses in dogs on a cumulative mg/M$^2$ basis.

No evidence of depressed liver function was apparent, although this had been observed terminally in dogs given lethal doses of AB-163 [7]. Otherwise, the toxicity was similar to that reported in dogs, which consisted mainly in gastrointestinal and neurological toxicities.

Gastrointestinal toxicity (mainly nausea and vomiting) was seen at lower doses and over the short term, while neurotoxicity appeared to be somewhat cumulative and possibly more dose-limiting in patients kept on treatment for longer periods. In this regard, cholinesterase-inhibiting effects of methylated aziridine congeners have been documented [1] and a number of the side effects seen, such as excessive secretions, central nervous system stimulation, and abdominal pains, were probably mediated via this mechanism. We made no attempt to reverse such side effects with atropine, but this could be tried cautiously.

This drug lends itself to combination studies with radiation therapy because of its reported effect as a radiation potentiator in P 388 leukemia [10] and because of its minimal effects on marrow reserve. We are currently exploring this approach in a pilot study at our institution.

For phase II trial on a weekly schedule a dose of 300–400 mg/M$^2$/week is recommended. The partial response noted in this study indicates that the drug has antitumor activity at tolerable doses and therefore phase II study in a suitable patient population is recommended.

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