Clinical Phase I Study of Aclacinomycin A by Evaluation of an Intermittent Intravenous Administration Schedule

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ABSTRACT

Aclacinomycin A (ACM) is an anthracycline antibiotic recently introduced into clinical trials because of its reduced cardiac toxicity in animal models relative to Adriamycin and daunomycin. This Phase I study of ACM was conducted to determine a dose suitable for i.v. administration on an every-3-week schedule. Twenty-five adult patients with solid tumors were treated with doses of ACM ranging from 60 to 120 mg/sq m i.v. every 3 to 4 weeks. Myelosuppression was the dose-limiting toxicity, but the degree and timing of blood count depression were variable at each dose level. Nausea and vomiting were seen at myelosuppressive doses, but mucositis was rare. Alopecia was seen in approximately one-third of the patients. There was no acute cardiac toxicity, but cumulative cardiac injury could not be evaluated in this trial. There were no major objective responses in three patients who had measurable disease. The recommended doses of ACM for Phase II studies are 100 mg/sq m for good-risk patients and 80 mg/sq m for patients who are heavily pretreated or who have a poor performance status.

INTRODUCTION

The anthracycline antibiotics, Adriamycin and daunomycin, are active antineoplastic compounds but produce both acute and dose-limiting cumulative cardiac toxicity (2) in addition to myelosuppression, alopecia, stomatitis, and acute gastrointestinal side effects (3). ACM1 is one of several new anthracyclines introduced into clinical trials with the goal of identifying an analog with an improved therapeutic index.

ACM was isolated from the broth of cultures of Streptomyces galilaeus (13). It possesses 3 sugars, rhodosamine, 2-deoxyfucose, and cinerulose, linked by glycosidic bonds and attached to the planar tetracyclic anthracyclic ring at C-7 (Chart 1). A potent inhibitor of nucleic acid and protein synthesis in cultured tumor cells, ACM is active against a spectrum of murine tumors including P388 leukemia, CD8F, mammary carcinoma, and colon tumor 38 (1, 11).

In large-animal toxicology studies, ACM produced vomiting, diarrhea, mucositis, anorexia, and fever and, with high doses, electrocardiographic and blood pressure changes (1). In the golden hamster model, ultrastructural changes in the heart are less frequent and less severe with ACM than with equivalent doses of Adriamycin, detorubicin, or AD-32 (4). The drug is extensively metabolized to both active and inactive compounds; metabolites are conjugated with sulfate and glucuronic acid and are measurable in bile and urine (12).

Clinical trials have been conducted in Japan and Europe using a spectrum of doses and schedules (6–10, 14, 15), with therapeutic responses being noted in patients with acute leukemia (8, 15), lymphoma (8–10), and a variety of solid tumors including cancers of the lung, breast, and stomach (6, 7, 9). Although an optimal dose schedule has not been clearly defined, in the above studies stomatitis and alopecia were rare; nausea and vomiting were mild to moderate; and only transient, minor electrocardiographic changes were noted. Myelosuppression and hepatocellular enzyme elevation were dose-limiting (9, 10, 14).

The present study was initiated in February 1980 to more clearly define the toxicity of ACM when given as a single i.v. injection every 3 weeks. This schedule was chosen because it is the most widely accepted schedule for Adriamycin use and because of its convenience for patients with solid tumors.

MATERIALS AND METHODS

All patients treated had a histologically or cytologically confirmed diagnosis of cancer refractory to conventional therapeutic modalities or for which no effective therapy is known. Patients had not been treated with radiation or chemotherapy during the 4 weeks prior to starting treatment with ACM. A performance status of at least 50% (Karnofsky scale), a life expectancy of at least 8 weeks, a WBC ≥4000/μl, a platelet count ≥150,000/μl, normal serum bilirubin (<1.5 mg/dl), and normal serum creatinine (<1.5 mg/dl) were required for entry into this study. Patients with a history of cardiac disease or prior therapy with >200-mg/sq m doses of anthracyclines were excluded from this trial. Informed consent was obtained from each patient prior to initiation of therapy. The characteristics of the 24 evaluable patients are presented in Table 1.

Each patient had an initial complete history and physical examination, chest radiograph, 12-lead electrocardiogram, and urinalysis. In addition, the following laboratory tests were obtained for each patient prior to treatment: CBC with WBC differential count, platelet count, reticulocyte count, prothrombin time, partial thromboplastin time, serum electrolytes, and a biochemical profile which included serum glucose, urea nitrogen, calcium, phosphorus, total protein, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase, and aspartate aminotransferase. Radionuclide scans of liver, bone, and brain were performed only when clinically indicated. Although this was a Phase I study, an attempt was made to identify evaluable parameters of disease in all patients; the absence of measurable lesions, however, did not exclude patients from this study.

Initially, ACM was given only to inpatients. However, as
experience with the drug and its toxicities was acquired, outpatient administration was also used. Inpatients were followed with daily CBC and platelet counts and biochemical profiles 3 times weekly. An electrocardiogram was performed within 1 hr of drug administration for inpatients. For outpatients, a CBC, platelet count, and biochemical profile were obtained once weekly. As the pattern of myelosuppression became better recognized, the frequency of CBC and platelet count determination was increased. When possible, tumor measurements were made once weekly. Appropriate radiological studies were repeated once monthly to evaluate tumor response.

Toxicity was graded on a scale of 0 to 3+, defined as follows: 1+ toxicity, mild, objectively present, but not disabling; 2+ toxicity, moderate, disabling but supportive management not necessary; and 3+ toxicity, severe, disabling, requiring hospitalization or special supportive therapy. Because one of the theoretical advantages of ACM over Adriamycin is the low incidence of alopecia, hair loss was graded as follows: 1+ alopecia, loss of less than 25% of hair; 2+ alopecia, loss of 25 to 50% of hair; and 3+ alopecia, loss of greater than 50% of hair. Alopecia was graded only for patients who had normal scalp hair at the time of initiation of therapy. Therapeutic responses were defined in accordance with standard criteria.

ACM was provided by the Division of Cancer Treatment, National Cancer Institute, Bethesda, Md., in 20-mg light-resistant vials containing ACM hydrochloride (20 mg), lactose (100 mg), and hydrochloric acid to adjust the pH. The drug was reconstituted with sodium chloride injection USP, providing a clear yellow solution with a 4-mg/ml concentration of ACM, and administered i.v. over 5 min through an established i.v. line.

The initial dose of ACM was 60 mg/sq m every 21 days; this is one-half the dose recommended by Ogawa (9) for Phase II studies. Dosage escalation was made by 20-mg/sq m increments through 120 mg/sq m. At least 3 patients were treated at each dosage level and evaluated for 3 weeks before other patients were entered on the next higher dosage level. The dose was repeated after 21 days in the absence of evidence of progressive disease or dose-limiting toxicity. If the WBC was less than 4000/μl or the platelet count was less than 100,000/μl on Day 22, therapy was withheld until hematological recovery was complete. Patients were considered evaluable for toxicity after one dose of ACM and 21 days of observation.

RESULTS

Twenty-five patients were entered into this study. One patient was considered inevaluable after a single dose of ACM because of early death related to progressive cancer. Twenty-four patients received a total of 52 doses of ACM. Thirteen patients received only one dose of the drug, but 8 patients received 3 or more doses, including 2 patients who each received 5 doses of ACM.

Toxicity. The dose-limiting toxicity was hematological, as indicated in Table 2. There was considerable variability in the hematological toxicity encountered within each dosage level. This appeared to be related, at least in part, to the extent of prior treatment, presence or absence of bone metastases, and performance status. Dose-limiting toxicity occurred in several patients in each of the 3 highest dose levels but, even at the highest dose level, one patient did not demonstrate any evidence of myelosuppression. Variability in the day of blood count nadir was noted as well. Thus, nadir counts may have been missed in some outpatients who had weekly blood count determinations. Generally, the platelet nadir occurred at approximately Day 10 after treatment and was followed by reduc-

![Chart 1. Structure of ACM.](chart1.png)

### Table 1

**ACM Phase I study: characteristics of 24 evaluable patients**

<table>
<thead>
<tr>
<th>Age</th>
<th>Median, 56yr</th>
<th>Range, 34–74yr</th>
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</thead>
<tbody>
<tr>
<td>Performance</td>
<td>Median, 70%</td>
<td>Range, 50–90%</td>
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<tr>
<td>Sex</td>
<td>Male, 9</td>
<td>Female, 15</td>
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<tr>
<td>Prior therapy</td>
<td>None, 1</td>
<td>Chemotherapy only, 7</td>
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<tr>
<td>Chemotherapy</td>
<td>Chemotherapy and radiotherapy, 6</td>
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<tr>
<td>Radiotherapy</td>
<td>Pathological diagnosis</td>
<td>Lung cancer, 10</td>
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<tr>
<td>Oat cell carcinoma, 1</td>
<td>Cervix cancer, 4</td>
<td>Adenocarcinoma, 2</td>
</tr>
<tr>
<td>Epidermoid carcinoma, 2</td>
<td>Breast cancer, 4</td>
<td>Head-neck epidermoid cancer, 2</td>
</tr>
<tr>
<td>Renal adenocarcinoma, 1</td>
<td>Malignant melanoma, 1</td>
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</table>

### Table 2

**ACM Phase I study: hematological toxicity**

<table>
<thead>
<tr>
<th>Dosage (mg/sq m)</th>
<th>No. of patients entered</th>
<th>No. of patients evaluable</th>
<th>WBC nadir × 10⁹</th>
<th>Platelet nadir × 10⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Median</td>
<td>Day</td>
<td>Range</td>
</tr>
<tr>
<td>60</td>
<td>6.6–10.2</td>
<td>8.0</td>
<td>13</td>
<td>188–339</td>
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<tr>
<td>80</td>
<td>2.0–11.1</td>
<td>2.7</td>
<td>21</td>
<td>64–514</td>
</tr>
<tr>
<td>100</td>
<td>1.5–5.4</td>
<td>3.0</td>
<td>18</td>
<td>25–500</td>
</tr>
<tr>
<td>120</td>
<td>0.1–7.2</td>
<td>2.5</td>
<td>15</td>
<td>23–317</td>
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</tbody>
</table>
tion of the WBC. The day of WBC nadir was more variable and occurred as late as 21 days following drug administration. Recovery from blood count suppression was rapid, usually occurring 4 to 6 days from the day of nadir. Myelosuppression did not appear to be cumulative in patients treated with more than 3 doses of ACM.

Patients frequently exhibited what appeared to be a transient "rebound" thrombocytosis following platelet depression by ACM. Nine patients in this trial had a maximum platelet count above 500,000/µl including 3 who had a maximum platelet count above 1,000,000/µl approximately 10 days following the platelet nadir. Although it cannot definitely be attributed to the ACM, this was a transient occurrence in all patients; it was temporally related to administration of ACM and therefore does not appear to represent a reactive thrombocytosis because of progressive tumor. Drug-related anemia or hemolysis were not observed during this trial. At the highest dose level, there was one death secondary to complications of sepsis that occurred temporally related to administration of ACM and therefore does not appear to represent a reactive thrombocytosis.

In addition to myelosuppression, the only other prominent toxicity was acute nausea and vomiting (Table 3). At doses that were myelosuppressive, the drug produced moderate nausea and vomiting, anorexia, and malaise, similar to that seen with Adriamycin. Mucositis and diarrhea occurred in only an occasional patient. Alopecia was noted in 5 of 14 patients who had scalp hair at the time the study was initiated. There was no evidence of acute cardiac injury in any of the patients. No extrasystoles were detected on electrocardiograms obtained within 1 hr of drug administration, and there were no S-T segment or T-wave changes. Nonetheless, several patients developed sinus tachycardias which may have been related to anxiety or associated with nausea and vomiting. No patient developed signs or symptoms of congestive heart failure; cardiac cineradioangiography was normal in 2 patients who received more than 400 mg of the drug per sq m.

Hepatic enzyme elevation and hyperbilirubinemia were not observed in any of the patients, nor was there any evidence of renal or pulmonary toxicity. Extravasation of ACM s.c. did not occur, and there were no episodes of inflammation at sites of drug injection or phlebitis in veins used for drug administration.

**Therapeutic Responses.** No objective responses were noted in the 2 patients with adenocarcinoma of the lung or one patient with melanoma who had measurable disease. One patient with multiple chest wall lesions from adenocarcinoma of the breast experienced partial healing of her lesions which lasted for 1 month.

**DISCUSSION**

ACM is one of a series of new anthracyclines that are being investigated in an attempt to find analogs of Adriamycin and daunomycin that have a better therapeutic index. In several animal systems, ACM appears to be less cardiotoxic than do other anthracyclines (3, 10). Furthermore, it appears that ACM has several other properties that distinguish it from other anthracycline antibiotics. Egorin et al. (5) demonstrated that, although cellular uptake of both ACM and daunomycin is dose dependent, the intracellular accumulation of ACM in cultured L1210 and P388 cells is approximately twice that of daunomycin at any given drug concentration. Whereas isolated cell nuclei accumulate more daunomycin, ACM is concentrated primarily in the cytoplasm. ACM is a more potent inhibitor of nucleic acid and protein synthesis than are either Adriamycin or daunomycin. Although both Adriamycin and ACM inhibit RNA synthesis at lower concentrations than are required to inhibit DNA synthesis, the difference is greater for ACM (11). In contrast, daunomycin is relatively more effective in inhibiting DNA synthesis (5). Additionally, the maximal effect of ACM is observed at the G1-S and S-G2 interfaces, in contrast to the blockade in early S phase seen with Adriamycin (1). Thus, in addition to its reduced cardiac toxicity, ACM may have a mechanism of action that differs in some details from the older anthracyclines.

In the clinical trials performed in Japan and Europe, most patients were treated with low individual doses of the drug given on a variety of schedules. There are 3 published reports of Phase I trials of ACM which include information on sequential dose escalation using a single dose schedule. Sakano et al. (14) reported that myelosuppression is dose limiting and that 70 mg/sq m was the maximal nontoxic dose; patients were not, however, treated with higher doses in their study. Ogawa et al. (9) observed that myelosuppression and hepatocellular enzyme elevation were dose limiting and recommended a dose of 100 to 120 mg/sq m for Phase II studies. However, only 4 of their patients were treated at that dose level. Oka studied several i.v. dose schedules including an intermittent schedule using 0.4 to 2.0 mg/kg every 3 weeks (10), but the available data are inadequate for determining an appropriate dose for further studies. Because the optimal dose for ACM administration every 3 weeks was not clearly established by these studies, a few studies were done using a single dose schedule. In the 2 patients with adenocarcinoma of the lung or one patient with melanoma who had measurable disease. One patient with multiple chest wall lesions from adenocarcinoma of the breast experienced partial healing of her lesions which lasted for 1 month.

**Table 3**

<table>
<thead>
<tr>
<th>Dosage (mg/sq m)</th>
<th>No. of evaluable patients</th>
<th>Grade of toxicity</th>
<th>Nausea and vomiting</th>
<th>Alopecia</th>
<th>Mucositis</th>
<th>Cardiac</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>5</td>
<td>1+</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>80</td>
<td>7</td>
<td>1+</td>
<td>2</td>
<td>1</td>
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<tr>
<td>100</td>
<td>9</td>
<td>1+</td>
<td>3</td>
<td>0</td>
<td>1</td>
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<td>0</td>
</tr>
<tr>
<td>120</td>
<td>6</td>
<td>1+</td>
<td>2+</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>1*</td>
</tr>
</tbody>
</table>

*a Diarrhea.

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the present trial was conducted.

ACM produces dose-limiting myelosuppression after single doses of 80 to 120 mg/sq m. Potentially life-threatening toxicity was observed in 2 heavily pretreated patients who received 100 mg/sq m. At 120 mg/sq m, one patient died as a result of drug toxicity. That dose cannot be recommended as a starting dose in Phase II trials. The degree and pattern of myelosuppression varied among the patients treated at each dose level, but hematological toxicity did not appear to be cumulative.

Cardiac toxicity was not observed in our patients, but the maximum dose given to any patient in this trial was 600 mg/sq m. Because electrocardiographic tracings were performed only on inpatients and because these recordings lasted approximately 1 min, it is possible that transient arrhythmias do occur acutely with ACM but were not detected. Determination of the incidence and extent of cardiac injury from ACM must await extended Phase II testing of the drug.

Alterations in liver enzymes and hyperbilirubinemia reported in the Japanese studies (9, 10, 14) were not seen in our patients. This may be related to the eligibility requirement in our study for normal hepatic function and possibly to the better performance status of our patients.

We recommend that the starting dose of ACM for Phase II studies be 80 mg/sq m i.v. every 3 to 4 weeks for patients with extensive prior therapy or a poor performance status. For patients with no or minimal prior therapy and a good performance status, the trial may be started at 100 mg/sq m. Since the timing of myelosuppression is variable, blood counts should be checked 8, 12, 15, 18, and 22 days after drug administration until the pattern of blood count suppression is established for each patient. In the absence of myelotoxicity, the dose may be increased by 20 mg/sq m. Although we have defined the acute and subacute toxicity following treatment with ACM, information regarding chronic toxicity cannot be obtained in a short-term Phase I study. Because the anticipated major advantage of ACM over older anthracyclines is reduced cardiotoxicity and since this is most likely to be a cumulative toxicity, careful attention should be given to monitoring of cardiac function repeatedly during extended Phase II studies.

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REFERENCES

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