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Aclacinomycin A in the treatment of multiple myeloma: A Southwest Oncology Group Study

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Summary

Fifty-two patients with progressive resistant multiple myeloma were entered in this Southwest Oncology Group Phase II study, using weekly intravenous Aclacinomycin A. Of forty-three evaluable patients for response, there was one partial remission of 2 years duration and two sustained clinical improvements with 25% reduction in paraprotein. Major toxicity seen was severe myelosuppression and significant nausea and vomiting requiring dose reduction and delay of the scheduled treatment. Cardiac arrhythmia was seen in one patient. Chronic daily schedule or continuous IV infusion is recommended for future study.

Introduction

Since the introduction of doxorubicin ten years ago, other new agents have only played a minor role in the treatment of refractory multiple myeloma. The natural and recombinant alpha-interferons have shown activity in refractory myeloma, but their precise role in the management of this subset of patients is as yet unclear [1].

Recent phase II studies using Aclacinomycin A, a new anthracycline antibiotic analog of doxorubicin, have shown significant antitumor effects in breast, ovarian, lung, and bladder cancers and in malignant lymphoma. A low incidence of cardiotoxicity and alopecia has been demonstrated [2]. Based on a report of 6 out of 9 responses of myeloma to Aclacinomycin A [3], the Southwest Oncology Group initiated a phase II trial to determine the antitumor activity of this agent in refractory myeloma.

Patients and methods

Fifty-two patients were registered. All had histologically confirmed multiple myeloma with progressive resistant disease, and had measurable disease, based on a monoclonal immunoglobulin spike in the serum and/or Bence-Jones proteinuria quantitated by urine electrophoresis. Prior treatment included alkylating agents, vincristine, nitrosourea and prednisone. Forty-two patients (80%) received doxorubicin. Pretreatment patient characteristics are presented in Table 1. Seventy-five percent of the patients had a Karnofsky performance status ≥ 50.

Treatment plan

This clinical trial was approved by the human experimentation committee within each institution and all patients agreed to participate in writing. Aclacinomycin A was provided by the Investiga-

Table 1. Pretreatment patient characteristics

Characteristics	Patients (n = 52)
Sex (M/F)	31/21
Performance status (Karnovsky)	
90–100	4 (8%)
70–80	15 (29%)
50–60	20 (38%)
30–40	13 (25%)
Type of multiple myeloma	
IgG	25 (48%)
IgA	17 (32%)
IgD	2 (4%)
Light chain	8 (16%)
Prior adriamycin	
yes	42 (80%)
no	10 (20%)

tional Drug Branch of the National Cancer Institute, Bethesda, Maryland. Aclacinomycin A was administered at an initial dose of 65 mg/m^2 by intravenous infusion over 20–30 minutes. Therapy was given weekly for four weeks, followed by a two week rest period. The initial dose and schedule was chosen based on our previous experience from a phase I study [4], which would be more practical to give on an out-patient basis rather than a daily intravenous schedule. Originally, if granulocyte count dropped below 1500 or platelets were less than 75,000, the subsequent weekly doses of Aclacinomycin A were decreased to 45 and 25 mg/m^2, respectively. Therapy was postponed for PMN < 500 or platelets below 50,000. However, due to significant myelosuppression in the first twenty-one patients treated, the starting dose for the next thirty patients was decreased to 50 mg/m^2. The subsequent dosage was reduced to 35 mg/m^2 if PMN was below 1000 or platelets < 75,000. Therapy was continued until there was evidence of progression of disease.

While on therapy, CBC and serum chemistry were monitored once a week and every four weeks respectively. EKG, MUGA scan or echocardiogram was obtained prestudy and every 3 months to monitor cardiotoxicity.

Response criteria

Complete response was defined as 1) a sustained decrease in a monoclonal peak of more than 75% of the initial value or 2) a quantitative light chain in the urine less than 10% of the pretreatment value or < 200 mg/24 hours for greater than 4 weeks. Partial response was defined as a 50–75% decline in the monoclonal peak or 10–50% of the pretreatment urine light chain. The response was considered "improved" if there was 25–50% reduction in the monoclonal peak or 50–75% of the pretreatment urine light chain. No response was defined as 75–100% of the pretreatment urine light chain or less than 25% reduction in cell mass after receiving at least two courses of Aclacinomycin A treatment.

Results

Patient characteristics

Fifty-two patients were registered in this Southwest Oncology Group Phase II trial. Forty-three of these patients were fully evaluable for response to treatment after receiving four full doses. Forty-seven patients were evaluable for toxicity and five patients were considered non-evaluable because of early death (i.e. within the first month of Aclacinomycin therapy).

Response data

Of the forty-three fully evaluable patients for response, only one achieved a partial remission with aclacinomycin therapy. This was a 65 year old black female who had stage III lambda light chain myeloma, initially presenting with T8 cord compression. A two year complete remission was obtained after therapy with melphalan, cyclophosphamide, vincristine, and prednisone alternating with doxorubicin, BCNU, vincristine and prednisone. At the time of recurrence, she had 2.9 grams of urine lambda light chain in 24 hours. The daily urine light chain dropped to 1.1 grams after 6 months of treatment which subsequently decreased below 500 mg/24

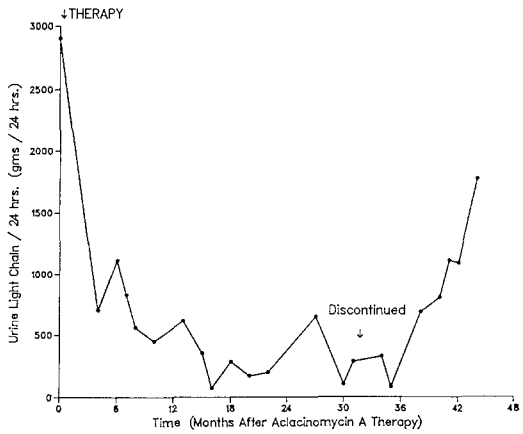

Fig. 1. The level of urinary light chain concentration in response to Aclacinomycin therapy.

hours and maintained at that level for the next 2 years while continuing on the same therapy (Fig. 1). Repeated MUGA scan during this time showed no changes in her left ventricular function. The patient received a total of 22 courses of aclacinomycin over a 32 month period. The disease recurred 4 months after discontinuation of treatment and responded again to combination chemotherapy of cyclophosphamide, melphalan and prednisone. She is currently doing well on therapy. Two additional patients considered "improved" had achieved 25% reduction in serum M-component concentrations and marked reduction in bone pain with improvement of anemia and performance status. Of the remaining for patients, twelve patients showed no progression while on therapy, twenty-eight showed evidence of progressive disease.

One of the three partially evaluable patients had 30% reduction of serum IgG monoclonal peak after 3 weekly doses, but the therapy was discontinued due to intractable nausea and vomiting. One additional patient, who required RBC transfusions for the anemia secondary to myeloma, showed a significant rise in the hemoglobin and did not require any more blood transfusions while receiving Aclacinomycin A even though there was no change in the M-component.

Toxicity

The major dose-limiting toxicities were severe nausea, vomiting and myelosuppression. The median nadir white count was 1900/mm^3 (range, 500–6600/mm^3) and the median nadir platelet count was 60,000/mm^3 (range, 13,000–250,000/mm^3). Twenty percent of patients experienced either severe leukopenia or life-threatening infection. Gastrointestinal toxicity and myelosuppression resulted in delay of scheduled treatments in about 30% of our patients. There was no evidence of phlebitis, skin or mucous membrane toxicity. Alopecia was difficult to evaluate due to incomplete reporting because some of the patients had alopecia from prior therapy. There were no drug-induced deaths. Out of eight patients who received therapy longer than three months, no congestive heart failure or cardiomyopathy was observed. The PR patient who received a cumulative dose of aclacinomycin of 2400 mg/M^2 developed atrial and ventricular ectopic beats responded to disopyramide phosphate. The arrhythmia resolved after the drug was discontinued.

Discussion

It is difficult to evaluate the antitumor activity of new agents for the treatment of multiple myeloma, since multiple agents are commonly used for induction, leading to multiple drug resistance. In this phase II study, Aclacinomycin A exhibited only a 2.3% objective partial response rate, and a 4.6% clinical improvement in heavily pretreated patients. The number of patients not previously treated with doxorubicin is too small to allow analysis as a subgroup. However, it should be noted that three patients who did respond had received prior doxorubicin. Forty percent of the patients experienced significant delay in their planned treatments, secondary to myelosuppression. Only seven patients with stable disease while on therapy were able to continue the treatment longer than three months.

Since the total planned dosage is similar to that used in the Japanese study reported by Sezaki [3], it is important to compare the two studies, taking

into account the different administration schedules and response criteria. In their study, patients received Aclacinomycin A by IV infusion at a daily dose of 15–25 mg/m^2 for 7 days every three weeks. Fifty-five percent (5 of 9) of those previously treated responded (reduction of M-protein 25% – >50%). Of these, only one would be considered a partial remission using our criteria. It should be noted that the Japanese administration schedule allowed the delivery of the same amount of drug in a shorter time with less toxicity. Another phase II study in acute leukemia using chronic daily IV administration of 15 mg/M^2 to the point of maximum tolerable amount had shown 38% complete remission in untreated patients and 17% complete remission in previously treated group [5]. Increasing response rate was also noted in patients who received a total dose of more than 200–300 mg/M^2.

In our study, aclacinomycin exhibited only minimal activity. However, the patient population had been heavily exposed to multiple drugs, and the planned treatment schedule was clinically very difficult to maintain. If future trials using this drug are to be considered, a chronic daily schedule as reported by Sezaki and Yamada [3,5] should be utilized. However, with such a schedule, hospitalization and prolonged supportive care during myelosuppression would likely be required. The higher response rate in a recent study using continuous infusion of vincristine, adriamycin and oral high dose Dexamethasone also made it attractive to study the continuous schedule in addition to chronic daily IV infusion for 1 hour, since it appeared to produce greater cell kill and allowed larger dose to be delivered with less toxicity [6]. Increasing the duration of infusion may also reduce nausea and vomiting seen with IV bolus.

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References

1. Oken MM, Kyle RA, Kay NE, Greipp PR, O'Connell MJ: A phase II trial of interferon alpha 2 in the treatment of resistant multiple myeloma. (Abstr) Proc Am Soc Clin Oncol 4:215, 1985
2. Oki T, Takeuchi T, Oka S, Umezawa H: new anthracycline antibiotic Aclacinomycin A: Experimental studies and correlations with clinical trials. Recent Results Cancer Res 76:21–40, 1981
3. Sezaki T, Adachi T, Ishii H, Asano K, Takahashi I, Kimura I: Aclarubicin in the treatment of multiple myeloma. Jpn J Clin Oncol 14:353–358, 1984
4. Karanes C, Young JD, Samson MK, Smith LB, Franco LA, Baker LH: Phase I trial of Aclacinomycin-A, a clinical and pharmacokinetic study. Invest New Drugs 1:173–179, 1983
5. Yamada K, Nakamura T, Tsuruo T, Kitahara T, Maekawa T, Uzaka Y, Kurita S, Masaoka T, Takaku F, Hirota Y, Amaki I, Osamura S, Ito M, Nakano N, Ogura M, Inagaki J, Onozawa K: A phase II study of aclacinomycin A in acute leukemia in adults. Cancer Treat Rev 7:177–182, 1980
6. Barlogie B, Smith L, Alexanian R: Effective treatment of advanced multiple myeloma refractory to alkylating agents. New Eng J Med 310:1353–1356, 1984

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