Cancer Chemother. Pharmacol. 4, 195–197 (1980)

Cancer Chemotherapy and Pharmacology

Actinomycin D in the Treatment of Advanced Breast Cancer

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Summary. *Actinomycin D is generally administered by serial low-dose injection over 5–10 days. Recent recognition of prolonged serum and tissue half-lives suggests that high-dose intermittent injection should be equally effective and less toxic. An intermittent single dose schedule was selected for this phase II trial of actinomycin D in 23 patients with advanced breast cancer refractory to standard combination chemotherapy. The drug was given in doses of 0.75–1.5 mg/m² at 2-week intervals or on days 1 and 8 of 28-day treatment cycles. One patient obtained a partial response with a duration of 5.7 months. Four patients experienced stabilization of advanced disease, with a mean duration of response of 6.4 months. Gastrointestinal toxicity occurred in 47% of patients and mild to moderate myelosuppression in 39%. We conclude that actinomycin D in this dosage and schedule has limited activity in advanced breast cancer. Higher doses might result in increased response rates but would be associated with greater toxicity.*

Introduction

Actinomycin D has been used as a chemotherapeutic agent since 1940 and has found a role in the treatment of Wilm's tumor, soft-tissue sarcomas, testicular cancer, and lymphomas. Despite occasional early reports of activity this agent has been used only sparingly in breast cancer and its efficacy is unknown.

Livingston and Carter [3] compiled five series and found five responders among 45 patients treated with actinomycin D. Four of these were reported by Watne [5] in a series of 18 patients given approximately 75 μg per kg body wt. over 5–10 days. The mean duration of the four partial remissions was 3.2 months and one toxic death occurred.

Serial low-dose injection of actinomycin D for 5–10 days in total doses ranging between 2.5 and 4.5 mg has been the standard method of administration based on previous reports of a very brief serum half-life. Newer pharmacologic data indicate that actinomycin D has a biphasic disappearance curve from the serum with a slow phase serum half-life of 36 h in humans [4] and a tissue half-life of 47 h in three animal species [1]. This suggests that an intermittent high-dose schedule should be as effective and less toxic than daily low doses.

The Oncology Research Center of the Bowman Gray School of Medicine undertook a phase II trial of this agent in advanced breast cancer patients refractory to standard combination chemotherapy. Intermediate doses were selected for this study since all patients had been heavily pretreated with aggresive chemotherapy and most had also received radiation therapy resulting in decreased bone marrow reserves.

Materials and Methods

Twenty-four patients with advanced breast cancer refractory to standard combination chemotherapy were treated with actinomycin D. Of these patients, 83% had also received radiation therapy and 65% had failed to respond to hormonal manipulation. Patient characteristics are presented in Table 1. One patient refused further treatment after one dose because of prolonged nausea and vomiting and is considered inevaluable. Six patients received actinomycin D on days 1 and 8 of 28-day treatment cycles; 17 patients received the drug at 2-week intervals. Patients were initially treated with 1.0 mg/m², which was escalated to 1.5 mg/m² after two doses if no hematologic toxicity occurred (white cell count over 4,000/mm³ and platelet count over 100,000/mm³ before next dose). Patients who had received radiation to the spine, pelvis, or sternum began with 0.75 mg/m² and this was escalated to full doses if there was no myelosuppression.

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0344-5704/80/0004/0195/$ 01.00

Table 1. Pretreatment characteristics

	No.	(%)
Evaluable patients	23	(100)
Age > 50	16	(70)
Disease-free interval < 2 years	15	(65)
Ambulatory > 50% of time	16	(70)
Prior therapy		
Surgery	22	(95)
Radiation	19	(83)
Hormonal	15	(65)
Chemotherapy		
Adriamycin® combination[a]	17	(74)
CMF combination[b]	10	(43)
Other combination	5	(21)
Single agent	3	(13)
Distribution of metastasis		
Soft tissue only	1	(4)
Bone (± above)	10	(44)
Brain, liver, lung (± above)	10	(44)
Other	2	(23)
Doses of actinomycin		
2–4	15	(65)
> 4	8	(34)
Mean/Range	5.2/2–18	

[a] Two or more drugs including Adriamycin®

[b] Cyclophosphamide, methotrexate, and 5-fluorouracil alone or in combination with other agents excluding Adriamycin®

All patients received at least two doses; the mean number of doses received was 5.2 per patient. CBC and platelet counts were obtained prior to each course of therapy.

Responses were judged by the criteria described by the International Union Against Cancer [2].

Results

One patient had a partial response and four others stabilized on this regimen; their disease characteristics and duration of response are given on Table 2. When standard combination chemotherapy was discontinued the responding patient had supraclavicular adenopathy, a pelvic mass, and symptomatic brain metastases. Radiation therapy was given to the cerebral lesion with good results. The pelvic disease (ovarian metastases and positive periaortic nodes) was completely resected prior to the start of therapy with actinomycin D. On therapy the supraclavicular adenopathy resolved and the neurologic signs and pelvic examination remained normal for 5.7 months, when CNS symptoms and supraclavicular adenopathy recurred simultaneously.

Two of the stable patients had only bone disease and were judged to be stable clinically and by radionuclide scans for 10.5 and 6.1 months before osseous metastases progressed. A third patient showed stabilization of bone disease and improvement in liver function tests and improvement in liver scan abnormalities lasting 6.3 months before new bone lesions appeared. The liver enzymes were normal and the liver scan continued to appear improved when therapy was altered. Because she had a long history of intermittent alcohol abuse, we cannot reliably conclude that this patient had a positive response to actinomycin D. The fourth patient had both bone and subcutaneous disease. Her bone disease remained stable for 2.6 months, when she was found to have new subcutaneous nodules.

The remaining 18 patients had rapidly progressive disease. The median survival of this group was less than 4 months.

Toxicity

The drug regimen was generally well tolerated, although nausea and vomiting were reported in 47% of the patients and one patient refused further therapy because of it. Dose escalation was precluded by nausea and vomiting in one patient. Only one patient experienced dermatitis, and radiation recall phenomena were not seen.

Table 2. Characteristics of stable and responding patients

Patient	Response	Duration (months)	Ambulatory > 50% of time	Prior chemotherapy[a]	Disease sites
1	Partial	5.7	Yes	CAF	Brain, pelvis, lymphatic system
2	Stable	6.1	No	CAVFP	Bone
3	Stable	10.5	Yes	CAVFP, M, Th, VL, CCNU	Bone
4	Stable	6.3	Yes	CMF	Bone, liver
5	Stable	2.6	Yes	CAVFP	Intraabdominal, subcutaneous, bone

[a] C, cyclophosphamide; A, Adriamycin®; F, 5-fluorouracil; V, vincristine; P, prednisone; M, methotrexate; Th, thioguanine; Vl, vinblastine

Moderate leukopenia in the 1,000–4,000/mm^3 range occurred in nine patients, or 39%. No thrombocytopenia occurred. No patient died of sepsis secondary to chemotherapy.

Comment and Discussion

While this intermittent schedule of intermediate dose actinomycin D was associated with moderate toxicity, only one of 23 patients showed an objective response that could be reliably attributed to the therapy. The significance of stable disease' in this setting is difficult to determine, but its duration (mean 6.4 months) in four patients with far advanced disease does suggest a pharmacologic effect.

The dose of 1.5 mg/m^2 is comparable to the most commonly used regimen of 0.5 mg daily for 5 days. Higher dosage schedules might result in an improved response rate; however, the responding patient and one of the stable patients continued to receive a dose of only 1 mg/m^2 because of hematologic toxicity. The incidence of hematologic toxicity in this study exceeded that in Watne's study (28%) despite the fact that our doses were lower. Responses were not more frequent in patients who experienced more severe toxicity and there is no convincing evidence that increased dosage would lead to an increased response rate and duration.

Using a moderate dose intermittent schedule of actinomycin D, we have observed one objective response and stability of advanced disease in four patients. Higher-dose regimens of actinomycin D might improve the response rate but would probably be accompanied by prohibitive toxicity. We conclude that actinomycin D in this dosage has limited activity in advanced breast cancer when used after first-line polychemotherapy.

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Received December 17, 1979/Accepted January 14, 1980