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Evaluation of amonafide in refractory and relapsing multiple myeloma: a Southwest Oncology Group study

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This study involved the administration of amonafide intravenously 300 mg/m² daily times five days every three weeks to 16 refractory and relapsed myeloma patients. Doses were esclated to toxicity. These doses caused severe thrombocytopenia and granulocytopenia in seven patients. No responses were seen in this heavily pretreated group of patients.

Key words: Amonafide, antineoplastic, chemotherapy, multiple myeloma.

Introduction

Amonafide is a 5-substituted benziosoquinolinedione. It is one of a new series of antineoplastic agents originally synthesized from imide derivatives of 3-nitro-1,8-napthalic acid.[1,2] Amonafide appears to function as a DNA intercalating agent.[3–6] In pre-clinical trials significant activity against two implanted murine leukemias, L1210 and P388, was noted. Two non-leukemic implanted murine tumors, M5076 sarcoma and D16 melanoma, were shown to be responsive.

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In phase I trials in single dose schedules and daily times five every 21 days myelosuppression was the dose-limiting toxicity, particularly granulocytopenia and thrombocytopenia. Cumulative myelosuppression was noted and recovery was reversible by day 21. Other toxicity included transient skin rash and mild phlebitis at the infusion site. Additionally, warmth, sweating, flushing, dizziness, headache, dyspnea, diaphoresis, nausea and vomiting occurred at the time of drug infusion. Hepatic, renal and cardiac toxicity were not observed.[7,8] To determine its activity in patients with relapsing or resistant multiple myeloma the Southwest Oncology Group initiated this phase II trial (SWOG 8726).

Material

Seventeen patients with relapsing or resistant myeloma were entered in this study. One patient was deemed ineligible because a pre-registration granulocyte count was less than required. Eligible patients had intermediate or high tumor mass myeloma which had been either refractory or had responded and relapsed after a single prior chemotherapy program. Patients were required to have a measurable paraprotein in the urine or serum or easily measurable plasmacytoma, a life expectancy of 8 weeks and a SWOG performance status of 0–2 (Karnofsky scale of 50–100). Pre-treatment laboratory studies required granulocytes greater than 1500/μl and platelets greater than 100 000/μl unless the lower counts were due

to marrow replacement with myeloma. The serum bilirubin had to be less than 1.5 mg/dl, the SGOT less than three times institutional normal and serum creatinine less than 2 mg/dl. The protocol was reviewed and approved by all Institutional Review Boards. An informed consent was required. Radiation therapy was allowed to limited areas for cord compression or impending fracture during the chemotherapy and corticosteroids were available at initiation for hypercalcemia. The appearance of these problems subsequent to the initiation of chemotherapy was considered to represent progression.

Patients received an initial dose of amonafide 300 mg/m^2 i.v. over 1 h on days 1–5. The drug was recycled on day 21 if, on that day, the platelets were 100 000 and the granulocytes 1500 and the patient had recovered from other toxicities. Treatment was continued until tumor progression, unacceptable toxicity or patient directed withdrawal.

Doses were decreased two levels for nadir platelet counts of less than 25 000 or granulocyte counts of less than 250 and by one level for platelet nadirs of 25 000–49 999 and/or granulocyte nadirs of 250–499. Doses were increased by one level if platelets did not fall below 100 000 or granulocytes below 1500, and were left unchanged when platelet nadirs were 50 000–100 000 and granulocyte nadirs 500–1500. If chest pain and flushing were noted the infusion was stopped and resumed at a lower dose rate. If chest pain and flushing continued at a lower dose rate the infusions were discontinued. The drug was held and the study co-ordinators notified for a serum bilirubin of greater than 2 mg/dl, creatinine greater than 2 mg/dl or SGOT of three times baseline.

Pre-study clinical requirements included a physical evaluation, weight, performance status, estimation of tumor mass, chest X-ray and skeletal X-rays as needed for tumor measurement. Laboratory requirements included quantitative measurements of myeloma immunoglobulins in the serum and or urine, serum beta II microglobulin, and bone marrow examination. CBC, serum creatinine, bilirubin, SGOT, calcium, uric acid, and alkaline phosphatase were required at initiation. Myeloma protein parameters were repeated every 6 weeks. With each cycle of drug the history, weight and performance exam, toxicity notation, a CBC, differential, platelets, creatinine, bilirubin and SGOT were required. A CBC and toxicity notation were required on week 2 of each cycle.

The standard SWOG myeloma measurements were used to determine response. Responsiveness was defined as a sustained decrease in the production rate of myeloma proteins by nephrolometry or electrophoresis to 50% or less of the pre-treatment value on at least two measurements at 3 week intervals. If plasma and urine proteins were present both must fall. Additionally, there must be no increase in the size or number of lytic bone lesions and the serum calcium must remain normal. Confirmatory support is given by recalcification of lytic bone lesions, significant increase in depressed normal immunoglobulins or a fall in the serum beta II microglobulin to normal levels. Patients were considered improved if there were declines in the serum myeloma protein production of less than 50% but not less than 25% of the pre-treatment level. Patients were considered unresponsive if there were lesser decline in protein values.

Relapse was indicated by an increase of more than 100% from the lowest level of serum myeloma protein production and increase above the remission level of the myeloma peak, i.e. relapse to more than 50% of the control myeloma protein production, a reappearance of peaks that have disappeared. Progression in bone disease was considered relapse.

Results

Sixteen eligible patients were entered on the trial and received a total of 45 cycles of amonafide. One patient received 18 cycles. Patient characteristics are listed in Table 1. There were four resistant and 12 relapsing patients, 13 high and three intermediate tumor mass patients. Most of the patients were vigorously treated with VCAP and VBAP on a previous SWOG protocol.

Grade IV thrombocytopenia and granulocytopenia were seen in seven instances (Table 2). One instance of grade IV neurologic toxicity was reported and two patients developed renal insufficiency not attributed to amonafide. All other toxicities were grade I or II and were infrequent.

Of the seven patients who experienced grade IV hematologic toxicity one also had grade IV neurologic toxicity. This patient became lethargic on the fifth day of treatment. By day 9 he was disoriented and combative. By day 12 he was comatose and on day 18 expired. It was felt by the investigator that his death was due to sepsis. His nadir white count was 1100/ml with 39

Table 1. Patient characteristics

	Amonafide ($n = 16$)	%
Age		
Median	61.5	
Minimum	44	
Maximum	71	
Sex		
Male	11	69
Female	5	31
Race		
White	14	88
Black	2	13
Other	0	0
Tumor mass		
High	13	81
Intermediate	3	19
Prior response		
Resistant	4	25
Relapsing	12	75

Table 2. Number of patients with a given type and degree of toxicity

Toxicity	Amonafide ($n = 16$) Grade					
	0	1	2	3	4	5
Anemia	15	0	0	1	0	0
Dizziness/hot flashes	15	1	0	0	0	0
General neurologic	15	0	0	0	1	0
Granulocytopenia	11	1	0	1	3	0
Headache	14	2	0	0	0	0
Leukopenia	2	1	5	5	3	0
Nausea/vomiting/anorexia	9	5	1	1	0	0
Renal/other	14	1	1	0	0	0
Thrombocytopenia	7	0	3	2	4	0
Venous sclerosis/phlebitis	15	0	1	0	0	0
Misc. other	12	3	1	0	0	0
Maximum grade any toxicity						
Number	1	1	2	5	7	0

neutrophils and 12 bands and the platelet count 19 000/μl.

Two patients developed renal insufficiency following the use of amonafide. One patient's failure was attributed to multiple myeloma. The serum creatinine rose to 3 mg/dl (grade II) on day 5 of the first cycle, from a baseline of 1.3 mg/dl at the start of therapy. His pre-therapy IgG was 15 g/dl. The second patient who developed an increased creatinine began therapy with a serum creatinine of 1.6 mg/dl which rose to 2.7 mg/dl on week 5 at the beginning of his second cycle of therapy. The creatinine rose further during that cycle to 4.6 (grade III). A consulting nephrologist felt that this was pre-renal due to sepsis, antihypertensives, and tobramycin rather than to amonafide. The serum creatinine fell to 3.1 mg/dl when the patient was taken off-study.

Responses

Five patients died or were taken off-study due to progression or toxicity after one course of amonafide. One patient remained with stable disease on treatment for 67 weeks. No anti-tumor responses to therapy with amonafide were observed in the myeloma patients studied.

Discussion

Amonafide was selected for clinical trial in myeloma because it had demonstrated pre-clinical activity in hematologic and solid tumors and because it had exhibited some anti-tumor activity in slow-growth solid tumors (e.g. prostate cancer) in phase I clinical trials. Most patients on this study received only one or two cycles of amonafide as a result of either toxicity or disease progression. Based on this study, it appears unlikely that amonafide will have significant anti-tumor effects in previously treated patients with multiple myeloma.

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