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Evaluation of Tryptophan Mustard (NSC-62403) in Patients with Plasmacytic Myeloma

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SUMMARY

Tryptophan mustard, 0.3 mg/kg i.v. once weekly, was given to 38 patients with plasmacytic myeloma. Of these, 27 were treated for 30 days or more and therefore were considered to be eligible for evaluation of response. Improvement in one or more parameters occurred in 14 patients. Six patients received benefit in two parameters or more. Toxicity consisted of leukopenia and thrombocytopenia but this did not cause serious complications. Nausea and vomiting occurred in 18 patients and necessitated cessation of therapy in 4. Tryptophan mustard appears to possess activity against plasmacytic myeloma and may be useful when other therapy has failed.

INTRODUCTION

Tryptophan mustard (5-bis-(2-chlorethyl)-amino-DL-tryptophan) was synthesized by DeGraw and Goodman (5) in 1962 and was soon shown to be active against various animal tumor systems (1, 14). This agent was first used in man by Fishbein *et al.* (6) who treated 26 cases of metastatic, nonleukemic neoplasms; no cases of plasmacytic myeloma were included. They found no decrease in tumor size, but considerable nausea, vomiting, leukopenia, and thrombocytopenia occurred. Oral administration of tryptophan mustard at seven times the weekly tolerated intravenous dose produced no toxicity.

MATERIALS AND METHODS

All patients fulfilled one of the following 2 criteria for the diagnosis of plasmacytic myeloma: (*a*) the bone marrow contained plasma or myeloma cells in excess of 40% and there was clinical disease compatible with the diagnosis; or (*b*) plasma or myeloma cells were in excess of 10% in the bone marrow or there were soft tissue masses histologically compatible with the diagnosis of plasmacytic myeloma plus at least one of the following: myeloma protein demonstrated in serum by electrophoresis on filter paper or cellulose acetate, myeloma protein demonstrated in urine by filter paper or cellulose acetate electrophoresis, or roentgenologic evidence of characteristic osteolytic lesions. In addition, other diseases which can be characterized by plasmacytosis in the bone marrow, such as collagen diseases, metastatic carcinoma, and cirrhosis, were absent.

Those patients who fulfilled the criteria for the diagnosis of plasmacytic myeloma were randomly allocated to either the tryptophan mustard protocol or to another study to avoid having a biased sample. The performance of each patient was arbitrarily categorized as: 0, normal activity; 1, had mild symptoms, but was ambulatory; 2, in bed less than 50% of the waking time; 3, in bed more than 50% of the waking time; and 4, completely bedridden.

The initial evaluation included history, physical examination, laboratory studies (determinations of hemoglobin or hematocrit value, leukocyte total and differential counts, platelet count, reticulocyte count, blood urea nitrogen [BUN] or blood urea, blood uric acid, and serum calcium; serum protein electrophoresis; urinalysis; examination for Bence Jones proteinuria; total protein determination and electrophoresis of a 24-hour urine specimen; and studies of bone marrow aspirates), and a roentgenographic skeletal survey. During therapy, determinations of hemoglobin or hematocrit values and leukocyte and platelet counts were repeated weekly; the serum electrophoresis and BUN were evaluated every 2 weeks, and urine electrophoresis and bone marrow aspirations were suggested every 4 weeks. All initial examinations were repeated when the study of each patient was terminated.

Evaluation of response was defined in the following parameters: (*a*) Hemoglobin: an increase of 2.0 gm/100 ml or more, persisting at least 2 weeks in the absence of recent blood transfusions, in those patients whose initial hemoglobin concentration was 11.0 gm/100 ml or less; or an increase in hematocrit value of 7% (initial level, 35% or less) under the same circumstances. (*b*) Serum globulin: decrease of 2.5 gm/100 ml or more from an

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TABLE 1
Dosage Schedule

Leukocytes (per cu mm)	Platelets (per cu mm)	Dose (% of standard dose)[a]
>5,000	>100,000	100
4,000–4,999		75
3,000–3,999	75,000–100,000	50
2,000–2,999		25
<2,000	<75,000	0

[a] Standard dose: 0.3 mg/kg body weight/week.

initial value of more than 4.5, or a return to normal values. (*c*) Urinary protein: decrease of at least 50% from an initial value of 1.0 gm/24 hr or more. (*d*) Plasma or myeloma cell: decrease of 500 per 1000 total marrow cells or a return to normal levels of plasma cells. (*e*) Recalcification of bone lesions and the absence of new lesions developing during the study. (*f*) Improvement of performance by two grades. (*g*) Decrease of pain by two grades (pain was graded on the basis of 0 to 4). Patients had to be treated for 30 days or more to be included in evaluation of response.

Tryptophan mustard, as the hydrochloride salt, was obtained as a dry powder (from Cancer Chemotherapy National Service Center), and it was dissolved in 5 to 10 ml of isotonic saline. This solution was injected intravenously within 10 minutes via the tubing of a running intravenous infusion of 5% glucose in water. The standard dosage was 0.3 mg per kilogram of body weight, given intravenously each week. This was altered according to Table 1.

RESULTS

Thirty-eight patients were entered in the study but 11 were not included in the final evaluation because they were treated for less than 30 days. Treatment was terminated in these 11 patients because of severe nausea and vomiting in four patients, death (the cause was not directly related to the drug) in four, presence of infection in two, and transfer to another hospital in one. Four of the 11 patients had infections (bronchopneumonia in two and septicemia and urinary tract infection in one each), but the leukocyte count was less than 3000 per cu mm in only one. Transient atrial fibrillation developed in one patient after intravenous injection of tryptophan mustard. Thus, definite drug toxicity (nausea and vomiting) was responsible for termination of therapy in only 4 of the 11 inadequately treated patients.

Results of therapy in the remaining 27 patients are shown in Table 2. There was response in 14 patients, with improvement in 2 or more parameters in 6 and in 1 parameter in the remaining 8.

Seventeen patients had received no chemotherapy or radiation before the present study; in these there were 14 separate responses to treatment in 9 patients. There were 12 separate responses in 5 patients among the 10 who had received previous therapy. This would suggest that response to tryptophan mustard was not more likely in previously untreated patients. Previous therapy given to 10 of our patients (Table 3) had been relatively ineffective, suggesting that some of our patients were resistant to conventional therapy. In seven patients the symptoms began more than 2 years before tryptophan mustard therapy was started; there were seven separate responses in these patients. Sixteen of the patients were treated within 3 months of the diagnosis of myeloma; in this group there were 12 separate responses. Thus, separate responses occurred at least as frequently in patients who had had their illnesses for a long time as in those diagnosed recently.

Four of the 18 patients who were anemic at the start of therapy had a significant increase in hemoglobin concentration or hematocrit value. The hemoglobin concentration or hematocrit value decreased in 20 patients during drug therapy.

The leukocyte count decreased to 3,000/cu mm or less in 24 of the 27 patients and to less than 2,000 in 10 of these patients. Two-thirds of the patients who developed leukopenia had had normal leukocyte levels (>5,000/cu mm) before therapy. The lowest leukocyte counts occurred between Day 15 and Day 45 in 15 patients. Four of the 27 patients developed an infection (pneumonitis, 3; furuncle, 1) during therapy but the leukocyte count was less than 3,000/cu mm in only one at the time of the infection.

Platelet counts of 75,000/cu mm or less occurred in 17 patients; the count was less than 50,000 in 8 of them. The initial platelet count was normal in all but four patients. The maximal thrombocytopenia occurred between Day 15 and Day 45 in 15 patients. Surprisingly, this level was not reached until after Day 90 in six patients. Bleeding was not a problem in any patient in spite of the thrombocytopenia.

The serum globulin concentration decreased by 2.5 gm/100 ml or more in 7 of the 20 patients with immunoglobulin peaks, but 1 had received plasmapheresis prior to chemotherapy. Six patients had no initial paraprotein peak. The urinary protein decreased by more than 50% in two of seven patients in whom it was evaluated. Significant decrease in plasma cells (500 per 1000 nucleated cells) occurred in 4 of the 6 patients in whom bone marrow differential counts showed more than 50% plasma cells prior to treatment. There was a decrease of plasma cells (200 per 1,000 nucleated cells) in seven patients. The remaining patients appeared to have no significant change in the plasma cell content of the marrow.

No healing of bone lesions was found in any patient. Bone lesions progressed in nine instances but the majority showed no change. Hypercalcemia improved in two patients without the benefit of corticosteroid therapy. Azotemia decreased in one patient during therapy and the BUN increased in two.

Pain decreased to some extent in 18 of the 22 patients who had had pain before treatment; it remained unchanged in 3 and became worse in 1. In six of these the pain was reduced by at least two grades. Two patients who were bedridden and unable to move because of pain were greatly relieved of pain after therapy was instituted. Performance improved to some degree in 17 of the 24 patients who had limitations of activity initially; the improvement was at least two grades in 4 of 15 patients with an initial grade of 2 or more. The performance became worse in four patients.

There was little correlation between the amount of drug given and the response (Table 4).

Duration of improvement varied from a few days to 20 months—the improvement was still present in seven (six pa-

TABLE 2

Results of Tryptophan Mustard Therapy of Multiple Myeloma

Patient No.	Age (yr.)	Sex[a]	Duration until therapy (mo.)		Previous therapy	NSC-62403		Results[b]									
			From onset	From diagnosis		Days	Dose (mg)	Hemoglobin (gm/100 ml)	Hematocrit (%)	Leukocytes (× 10^3/cu mm)	Platelets (×10^3/cu mm)	Serum protein[c] (gm/100 ml)	Urine protein (gm/24 hr)	Bence Jones	Plasma cells in marrow (%)	Pain[d]	Performance[d]
1	47	M	4	1	None	155	315	12.2		12.4	160				65		0
								12.2		2.7	58				*15*		1
2	55	M	9	3	Local RoRx	271	162	6.1		6.3	101	1.6/9.5	1.2	+	67	0–1	3
								11.8		2.0	23	2.9/*6.2*	*0.4*		*15*	0	*0*
3	61	F	3	0	None	593	415	12.3		4.6	171	2.6/7.7	0.3		39	3	4
								7.0		2.0	46	3.0/6.5	0.4	0	13	*1*	*1*
4	70	F	7	½	None	102	95	10.6	33	4.8	348	2.7/5.5			50	3	3
								5.9	17	2.5	50	2.8/5.2		+	55	1–2	2
5	72	F	16	2	None	196	144		28	5.6	324	4.0/1.6	9.0	+	81	2	2
									19	1.2	52	4.5/1.4	*3.3*		*3*	1	1
6	48	M	7	1	None	95	139	13.0		8.0	430	3.0/6.6	2.2	+	26	1–2	1
								11.5		3.4	124	3.9/*3.5*	2.0		24	0	0
7	73	M	36	0	None	40	76	7.5		7.7	206	2.6/3.0	0	0	47	3	4
								10.2		2.3	142	2.6/4.1	0		59	2	*2*
8	74	M	13	11	None	119	205	12.3		5.3	286	4.0/7.6	0.13		20	3	1
								8.7		1.7	60	4.2/7.4			10	*1*	0
9	52	F	1	0	None	294	258	9.9		6.5	224	3.3/7.2	1.2	0	13	2	1
								13.0		2.2	114	5.0/*2.2*			0.5	*0*	0
10	58	M	18	0	None	41	130	10.4		7.8	330	2.8/3.4	0	0	8.9	0	0
								7.8		4.0	65	2.9/3.3	0		5.0	0	1
11	75	M	3	0	None	282	335		23[e]	5.3	162	2.9/9.0	0.02		67	1	1
									31	1.8	45	3.6/5.1[f]	0.25	0	60	0	1
12	62	M	2	1	None	99	179	15.2		10.1	357	4.6/2.1	2.3	0	0.6	1	1
								12.9		2.6	85		1.2		1.2	0	0
13	60	M	13	1	None	106	247	15.8		7.0	220	3.8/3.7	0	0	47	1	2
								11.3		2.5	63	4.0/4.0			7	1	1
14	46	M	3	0	None	112	235	12.4		9.9	130	3.5/7.1	3.5	0	28	2	3
								5.4		2.7	43	3.2/5.0	4.0		29	2	1–2
15	67	F	25	1	None	111	155		26	5.1	250	4.7/2.5	11	+	No change	1	1
									21	2.1	50	5.0/2.2	6.0			0	1
16	64	M	32	32	RoRx	84	92		30	6.7	90	3.2/3.6	0		20–40	3	2
									21	0.9	38	3.7/2.7			No change	*0*	1
17	70	M	53	33	RoRx, uracil mustard, L-PAM[g], cyclophosphamide	77	68		28	4.1	206	2.8/7.4	0.5	0	25	2	3
									27	1.1	82	4.3/6.7	0.2		10	1	2
18	43	M	8	6	RoRx, cyclophosphamide	79	68		19	3.6	67	4.8/8.0	0.8	+		1	2
									13	1.4	22	3.7/6.3	0.6		90	2	2
19	61	F	5	3	None	90	73		24	5.3	75	4.7/12.5	0.25	0	65	0	1
									15	2.5	75	5.5/*8.7*	0.12		35–40	0	1
20	49	F	5	1	None	35	60		39	5.0	220	4.6/1.3	0.4	0	50	2	2
									37	1.9	128	4.3/1.7	0.4		40	1	2
21	56	M	36	33	RoRx, L-PAM	197	373		33	13.3	371	3.7/6.9	?	+		4	4
									20	2.7	106	4.2/*2.0*		0		*1*	*2*
									35								

22	82	F	35	33	Amethopterin	42	66	8.6		3.7	50	No change			25	0	2–3
								5.4		2.0	30		0		31	0	4
23	67	M	22	10	L-PAM, cyclophosphamide	126	148		33	7.5	228	3.9/3.5	0	0	Packed	2	1
									32	1.4	74	3.9/2.9				*0*	0
24	71	M	2	0	None	90	95		19[e]	3.4	200	2.4/8.1	0.3	0	No change	0	2
									37	1.6	40	*4.4/5.5*	0.2			0	1
25	53	F	11	7	Amethopterin	77	94		23	4.5	184	3.0/6.8	0.1	0	65–70	2	2
									21	1.9	134	3.3/6.4	0		*15–20*	1	1
26	63	M	8	0	RoRx	70	70		32	3.7	254	3.5/5.6	1.8		?	0–1	0
									28	2.0	140	3.5/5.1	1.3			0	1
27	64	M	25	10	Amethopterin	75	243		39	6.1	240	3.1/6.5	0	0	Increased	1	1
									32	3.2	202	3.3/5.8				1	1

[a] All patients were Caucasian except Nos. 20 and 25 who were Negro.
[b] Data shown as pairs of numbers; upper value is initial finding, lower value is finding after therapy. *Italics* indicate a response to therapy.
[c] Shown as albumin/globulin.
[d] See text for explanation.
[e] Transfusions.
[f] Plasmapheresis.
[g] L-PAM, L-phenylalanine mustard.

TABLE 3

Results of Previous Therapy in 10 Patients

Type of therapy	Number of therapeutic trials	Benefit			Inadequate trial
		Questionable	Some	None	
Radiation	6	2	2	2	0
L-Phenylalanine mustard	3	0	0	2	1
Cyclophosphamide	3	0	0	2	1
Amethopterin	3	0	0	2	1
Uracil mustard	1	0	0	1	0

TABLE 4

Relationship Between Total Dose of Tryptophan Mustard and Number of Separate Responses

Total dose of drug (mg)	Number of separate responses
50–100	6
101–150	4
151–200	5
201–300	4
301–450	7

TABLE 5

Duration of Improvement With Tryptophan Mustard Therapy

Duration of improvement (days)	Parameters of improvement (case number)					
	Hemoglobin or hematocrit	Serum protein	Urine protein	Plasma cells in marrow	Pain	Performance
<30						7
31–60		2	5			
61–90	2	19,[a] 24		1[a]		
91–120	7		2		8	2
121–150				25		
151–180				2	16	
>180	9, 21[a]	6,[a] 9, 21[a]		5[a]	3, 9, 21, 23[a]	3, 21

[a] Improvement still present at time of report.

tients) of the 26 responses at the time of the present evaluation (Table 5).

Toxicity consisted of leukopenia and thrombocytopenia, which has been described. This was well-tolerated in the present study. Nausea and vomiting occurred in 18 of the 27 patients and was severe enough to require discontinuation of therapy in 4. In addition, nausea and vomiting caused termination of therapy in 4 of the 11 patients who received an inadequate trial of therapy. A gastric ulcer developed in one patient and did not heal until therapy was discontinued. Bronchospasm and hypotension occurred in one patient after intravenous administration of tryptophan mustard. Weight loss occurred in 20 patients during the therapeutic trial; 6 patients lost less than 10 pounds while 13 lost from 10 to 20 pounds.

DISCUSSION

The treatment of patients with plasmacytic myeloma is a difficult challenge and requires varied physical and drug therapeutic programs. Radiation therapy is helpful for localized lesions but, in most instances, the disease is too widespread for it to be of clinical value as the only mode of therapy. Despite early optimistic reports (10, 12), urethane has proved to be of little value in therapy of plasmacytic myeloma (7). L-Phenylalanine mustard (melphalan, L-sarcolysin, L-PAM, Alkeran) has produced clinical benefit in several studies. Bergsagel *et al.* (2) reported objective improvement in 14 of 24 myeloma patients treated with L-phenylalanine mustard, Costa (4) found objective response in 16 of 42 patients, and Brook *et al.* (3) stated that half of their 36 patients improved. Hoogstraten (8) saw objective benefit in two or more parameters in 54% of 65 patients treated with L-phenylalanine mustard. Speed and co-workers (13) found relief of pain in 11 of 15 patients, as well as objective improvement in the sedimentation rate, serum globulin, and serum calcium concentrations after melphalan therapy. Another alkylating agent, cyclophosphamide (Cytoxan), was reported (9) to produce improvement in 25% of 165 patients.

Tryptophan mustard has been shown (6) to have a higher level of antitumor activity than does nitrogen mustard (methyl-bis-(β-chloroethyl)-amine, Mustargen) in mice with plasma cell tumor YPC1. In fact, the agents producing the most clinical benefit in patients with myeloma—L-phenylalanine mustard, cyclophosphamide, and now tryptophan mustard—have been ring structures whereas nitrogen mustard, an aliphatic compound, has been of virtually no benefit. Furthermore, there is evidence to suggest that another ring compound, aniline mustard, is active against plasma cell tumors in mice (11, 15).

Toxicity with tryptophan mustard was significant and consisted of leukopenia and thrombocytopenia. Although this was of a considerable degree, few complications resulted. Nausea and vomiting were present in the majority of patients and were of sufficient severity to force cessation of therapy in 8 patients. This includes four of the patients treated less than 30 days.

It is of significance to find that some response to tryptophan mustard did occur in patients in whom conventional therapy had been ineffective. This would suggest that tryptophan mustard, in spite of its disadvantages, might be tried in those patients who fail to respond to L-phenylalanine mustard and cyclophosphamide. It also suggests that we should look for other ring compounds that may be even more specific than L-phenylalanine mustard or cyclophosphamide.

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