Contribution of Prednisone to the Effectiveness of Hexamethylmelamine in Multiple Myeloma[1,2]

Martin M. Oken,* Raymond E. Lenhard, Jr, Anastasios A. Tsiatis, John H. Glick, and Murray N. Silverstein[2]

The Eastern Cooperative Oncology Group evaluated hexamethylmelamine in 89 patients with advanced refractory or relapsing multiple myeloma. Hexamethylmelamine was initially used as a single agent administered orally at 200 mg/m^2/day for the first 3 weeks of each 4-week cycle. When this regimen proved to be ineffective, it was modified first by increasing the dose of hexamethylmelamine to 280 mg/m^2/day and subsequently by adding prednisone at 75 mg for the first 7 days of each 28-day cycle. None of the 39 patients receiving hexamethylmelamine without prednisone had an objective response, while two patients had minimal objective improvement (25%–50% decrease in M protein with symptomatic improvement). Only 14% of these patients had objective or symptomatic response or both. In contrast, patients treated with hexamethylmelamine plus prednisone had a 22% objective response rate, with another 14% showing lesser degrees of objective improvement. Fifty-one percent of the patients treated with this regimen had either objective or symptomatic improvement or both. Severe (grade 3) toxicity was seen in nearly two-thirds of the patients on the higher-dose hexamethylmelamine regimens compared with 37% of the patients receiving low-dose hexamethylmelamine; however, in most instances this represented rapidly reversible cytopenias. Because all but one of the patients responding to hexamethylmelamine plus prednisone had experienced previous treatment failure on regimens containing prednisone in similar dose and schedules, it is unlikely that the responses are due to prednisone alone. Instead, this study suggests that the activity of hexamethylmelamine in multiple myeloma is dependent on the concomitant administration of prednisone and that the combination regimen appears to be synergistic. [Cancer Treat Rep 71:807–811, 1987]

Only a limited number of drugs have proven effectiveness in chemotherapy for multiple myeloma. This represents a major obstacle to the treatment of refractory myeloma and to the improvement of primary treatment of this disease. The Eastern Cooperative Oncology Group (ECOG) conducted a study of hexamethylmelamine in the treatment of advanced refractory or relapsing multiple myeloma (EST-3477). This agent was selected for study, in part, because of its demonstrated activity in alkylating agent-resistant lymphomas (1–5). Although hexamethylmelamine is structurally related to triethylenemelamine, it does not appear to function as an alkylating agent (4–6). Thus, it represents a new class of drugs with potential for the treatment of multiple myeloma.

In this study hexamethylmelamine was initially used

[1] Received Sept 19, 1986; revised May 20, 1987; accepted May 28, 1987.

[2] This study was conducted by the Eastern Cooperative Oncology Group (*Paul P. Carbone*, chairman, CA-21115) and supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. The following members participated in the study: University of Minnesota, Minneapolis (*M. M. Oken*, CA-20365); The Johns Hopkins Oncology Center, Baltimore, MD (*R. E. Lenhard, Jr*, CA-16116); Dana-Farber Cancer Institute, Harvard School of Public Health, Boston, MA (*A. A. Tsiatis*, CA-23318); Hospital of the University of Pennsylvania, Philadelphia (*J. H. Glick*, CA-15488); and Mayo Clinic, Rochester, MN (*M. N. Silverstein*, CA-13650). Other participating institutions include: Albany Medical College, NY (CA-06594); Albert Einstein College of Medicine, Bronx, NY (CA-14958); American Oncologic Hospital, Philadelphia, PA (CA-18281); Brown University and Roger Williams General Hospital, Providence, RI (CA-15947); Case Western Reserve University, Cleveland, OH (CA-14548); Chicago Medical School, IL (CA-14144); Hahnemann Medical College, Philadelphia, PA (CA-13611); Harbor General Hospital, Torrance, CA (CA-21091); Medical College of Ohio, Toledo; New York University Medical Center, New York (CA-16395); Northwestern University Medical Center, Chicago, IL (CA-17145); Our Lady of Lourdes Hospital, Binghamton, NY; Pennsylvania Hospital, Philadelphia (CA-13613); University of Pittsburgh, PA (CA-18653); University of Rochester Cancer Center, NY (CA-11083); Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL (CA-25988); Tufts University, Walpole, MA (CA-07190); Natalie Warren Bryant Cancer Center, Tulsa, OK; and Wisconsin Clinical Cancer Center, Madison (CA-21076).

* *Reprint requests to:* Martin Oken, MD, Department of Medicine, Veterans Administration Medical Center, 54th Street and 48th Ave S, Minneapolis, MN 55417.

as a single agent administered at 200 mg/m^2/day for the first 3 weeks of each 4-week cycle. When only marginal activity of this regimen was demonstrated despite the report of convincing efficacy of another regimen which employed hexamethylmelamine at a higher dose with prednisone (7), the treatment schedule was amended, first by increasing the dose of hexamethylmelamine and subsequently by adding prednisone.

METHODS

Patients with an established diagnosis of multiple myeloma supported by the demonstration of a focal or generalized increase in plasma cells in the bone marrow and a monoclonal protein in the serum or urine, who were refractory to or relapsing from prior standard chemotherapy, were potentially eligible for this study. Other eligibility requirements included no antitumor chemotherapy for at least 4 weeks prior to study; adequate bone marrow, renal, and liver functions; and wbc count $> 2000/mm^3$, platelet count $> 50,000/mm^3$, creatinine < 2.0 mg/dl, and bilirubin < 1.5 mg/dl with no active liver disease.

Response was evaluated according to both objective and symptomatic criteria. A 50% decrease in serum M protein or a 90% decrease in 24-hour urine light-chain excretion in patients lacking serum M protein constituted an objective response. A 25%–49% decrease in serum myeloma protein or a 50%–90% decrease in 24-hour light-chain excretion in patients lacking serum myeloma protein was rated as objective improvement only if it was associated with a sustained symptomatic improvement. Symptomatic response required an unequivocal improvement in bone pain or improvement in performance status from chronically bedridden to ambulatory. This improvement must persist 4 weeks and not be attributable to supportive care. Toxicity was evaluated by ECOG standardized criteria (8).

Response rates between treatment regimens were statistically compared using Fisher's exact test (two-sided). Response curves were generated using the method of Kaplan and Meier and compared using the log-rank test.

Initially, hexamethylmelamine was administered as a single agent at 200 mg/m^2/day orally on Days 1–21 of each 28-day cycle (Regimen H). Subsequently, the regimen was modified by increasing the dose of hexamethylmelamine to 280 mg/m^2/day orally on Days 1–21 and pyridoxine at 100 mg orally three times a day was added (Regimen HP). The final modification (Regimen HPP) consisted of Regimen HP with the addition of prednisone at 75 mg orally on Days 1–7 for each 28-day cycle. Patients were treated to relapse or disease progression unless unacceptable toxicity or patient refusal caused earlier cessation of therapy. For the second and all subsequent treatment cycles the hexamethylmelamine dose was reduced by 25% if the wbc count was $< 4000/mm^3$ or the platelet count was $< 100,000/mm^3$ or by 50% if the wbc count was $< 3000/mm^3$ or the platelet count was $< 75,000/mm^3$.

Treatment was suspended for wbc count $< 2000/mm^3$ or platelet count $< 50,000/mm^3$ and not resumed until recovery above these levels occurred. Treatment was reduced by 50% for moderate neurotoxicity or sustained nausea and vomiting and was discontinued for severe neurotoxicity or intractable vomiting.

RESULTS

Of the 89 patients entered in this study, 80 were evaluable (table 1). Three patients were removed from study before starting therapy, while two others were ineligible because of platelet counts $< 50,000/mm^3$ at the time of entry. Four other patients were inevaluable because of major protocol violations. Five of the 80 evaluable patients could be evaluated for toxicity, survival, and symptomatic response but not for objective response because of the lack or inadequate follow-up of measurable disease. Patients were evaluable for symptomatic response only if they entered the study with marked bone pain or impaired performance status (bedridden). Therefore, 11 asymptomatic patients were excluded from this analysis. Sixty-five patients were evaluable for both objective and symptomatic response. The three patients who died during the first 30 days in the study were considered evaluable and counted as nonresponders. They included one patient treated with each regimen.

The patients treated on the three regimens are comparable with regard to age, extent of disease (9), number of prior treatment regimens, and prior response to therapy (table 1). Patients receiving the HP regimen included a greater proportion of women, whites, and patients with severe anemia. The severity and manifestations of skeletal disease were comparable on the three regimens except that no patient treated with the HP regimen was hypercalcemic prior to entry.

No patient receiving hexamethylmelamine without prednisone had an objective response (table 2), and only two had objective improvement. In contrast, eight patients who received the prednisone-containing HPP regimen had objective response and five additional patients in this group showed objective improvement. The overall objective response or improvement rate of 36% for the HPP regimen is superior to the 5% response rates in the H and HP regimens ($P = 0.001$). One patient who responded to the HPP regimen had steroid psychosis and received no further prednisone after the second cycle of chemotherapy. He had a 5-month objective response and was successfully reinduced to a second objective response on hexamethylmelamine alone. Examination of the 13 patients responding to HPP reveals that 12 of them had had prior treatment failure on regimens containing prednisone in doses and schedules similar to the prednisone used in this protocol: 75 mg/day on Days 1–7. In their treatment immediately preceding entry in this study, five of the responding patients on the HPP regimen had received regimens containing prednisone at 60 mg $\times$ 4–7 days each cycle, four received prednisone at 120 mg $\times$ 4 days each cycle, one re-

TABLE 1.—Patient characteristics

Characteristic	Regimen H	Regimen HP	Regimen HPP	Total
No. of patients—				
Entered	33	15	41	89
Eligible	32	15	40	87
Total evaluable	30	13	37	80
Evaluable for objective response	29	10	36	75
Pretreatment data*				
Average age in yrs (range)	64.0 (50–84)	60.8 (45–82)	63.0 (38–83)	
Patients > 70 yrs	23%	15%	19%	
Sex				
M	47%	23%	46%	
F	53%	77%	54%	
Estimated tumor burden				
Low	7%	8%	8%	
Intermediate	17%	23%	14%	
High	76%	69%	78%	
Severe anemia (Hgb < 8 g/dl)	37%	62%	35%	
Moderate to severe bone pain	67%	54%	59%	
Extensive skeletal disease	63%	62%	62%	
Hypercalcemia	13%	0%	14%	
Prior treatment				
≥ 2 regimens	67%	62%	70%	
Primary refractory (no prior response)	20%	23%	22%	

*80 evaluable patients.

ceived prednisone at 90 mg × 5 days each cycle, one received 75 mg × 7 days each cycle, and one received continuous prednisone at 30 mg/day for 3 months. These 12 patients all had progressive disease on their prednisone-containing regimens from 1 to 4 months prior to entry in this study (median, 2.0 months). One of the responding patients had received no prior corticosteroid therapy. It is possible that this patient's 1-month objective improvement was due to the prednisone alone. Ten of the responding patients had received two or more prior regimens. The three other patients were unresponsive to their only prior treatment which consisted of high-dose intermittent melphalan and prednisone (two patients) or the M2 protocol (one patient).

Symptomatic responses followed the same pattern as objective responses. Sixteen percent of the evaluable patients receiving hexamethylmelamine without prednisone had improvement of symptoms compared with 50% of patients receiving the HPP regimen ($P = 0.004$). Clinical benefit in the form of objective response, objective improvement, or symptomatic response was obtained in 13% of the patients treated with Regimen H, 15% of the patients treated with Regimen HP, and 51% of the patients treated with Regimen HPP. The median duration of objective response is 5 months, including three response durations of 15, 17, and 30+ months. The median duration of objective response and objective improvement is 4 months (range, 1–34). Symptomatic improvement lasted > 1 year in seven patients, of whom five were receiving Regimen HPP.

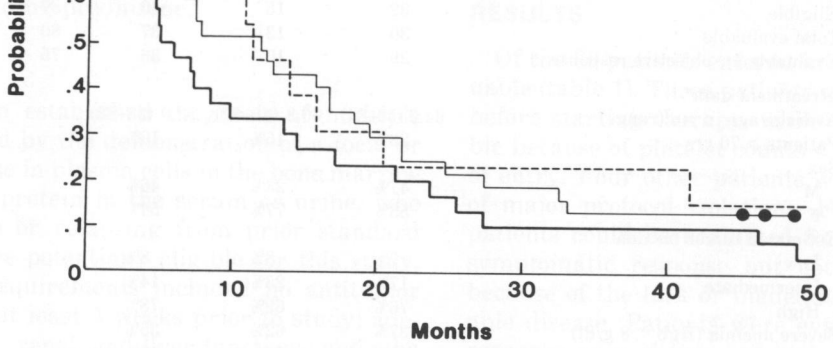
TABLE 2.—Response to therapy*

	Regimen H	Regimen HP	Regimen HPP
Evaluable	29	10	36
Objective response	0	0	8 (22)
Objective improvement with symptomatic response	1 (3)	1 (10)	5 (14)
No response	28 (97)	9 (90)	23 (64)

*Values = No. of patients (%).

The median survival of all evaluable patients was 9.6 months. The survival of the 80 patients by regimen is shown in figure 1. There are no significant differences when these curves are analyzed by log-rank test ($P = 0.32$). Furthermore, these data do not suggest that the addition of prednisone enhanced survival. The 1-year survival rate of the 25 patients with objective or symptomatic response was 76%. Their median survival was 19.5 months. The median survival of the eight patients with objective response was 17.9 months.

Severe toxicity (grade 3 or more) was seen in 37% of the patients with Regimen H compared with 69% and 62%, respectively, on patients treated with Regimens HP and HPP (table 3). The latter two regimens contain hexamethylmelamine at a 40% higher dose. Severe depression of the leukocyte or platelet count was two to three times more likely to occur on the high-dose hexamethylmelamine regimens as on the lower dose. A somewhat higher incidence of infection was seen on the HPP regimen; however, only 11% of patients had severe infections. Severe hemorrhage occurred in two patients, both receiving HPP. Nausea and vomiting was seen in



Treatment	Alive	Dead	Total	Median
H	0	30	30	5.4
HP	0	13	13	11.3
HPP	4	33	37	11.9

FIGURE 1.—Overall survival probability for all evaluable patients from start of chemotherapy.

about one-half of the patients and was severe in about 10%. Severe peripheral neuropathy was rarely encountered, but mild peripheral neuropathy was seen, particularly in patients receiving Regimen HPP, perhaps because this regimen has more responders who therefore received the treatment for a longer period of time. Nearly 25% of the patients experienced some CNS symptoms in the form of dizziness, tremor, or depression. There was no suggestion of decreased neurotoxicity in the two pyridoxine-containing regimens.

DISCUSSION

This study demonstrates that hexamethylmelamine has minimal activity in the treatment of multiple myeloma when used as a single agent. However, when hexamethylmelamine is combined with prednisone in an intermittent dose schedule, objective response or improvement may be obtained in one-third of the patients and symptomatic responses obtained in one-half. This finding confirms the report of Cohen and Bartolucci (10)

TABLE 3.—Toxicity*

	Regimen					
	H (n = 30)		HP (n = 13)		HPP (n = 37)	
Toxic effect	Grades 1-2	Grades 3-5	Grades 1-2	Grades 3-5	Grades 1-2	Grades 3-5
Maximum toxicity	50%	37%	31%	69%	32%	62%
Leukopenia	30%	10%	31%	31%	57%	30%
Thrombocytopenia	27%	10%	23%	23%	30%	24%
Infection	7%	7%	0%	15%	14%	11%
Nausea and vomiting	37%	10%	38%	15%	46%	11%
Neurotoxicity						
Peripheral neuropathy	3%	3%	15%	0%	32%	0%
CNS	17%	3%	23%	0%	16%	11%
Corticosteroids	0%	0%	0%	0%	11%	3%

*n = No. of patients. Toxicity grade: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; and 5 = lethal. Myelotoxicity: wbc count (cells/mm^3)—0 = $\geq$ 4500, 1 = 3000-4499, 2 = 2000-2999, 3 = 1000-1999, and 4 = $<$ 1000; platelet count (cells/mm^3)—0 = $\geq$ 130,000, 1 = 90,000-129,999, 3 = 50,000-89,999, and 4 = $<$ 50,000.

and, combined with their experience, represents the results of > 100 patients treated with essentially the same hexamethylmelamine plus prednisone regimen.

Before one can consider this as evidence of a synergistic antitumor effect of prednisone with hexamethylmelamine, the alternate proposition that some of the responses could have been caused by prednisone alone must be considered. Objective and symptomatic responses have been reported with higher and more frequent doses of prednisone in patients with no prior corticosteroid therapy (11) and in patients who had received prior corticosteroids in standard dosage (12). Frequent courses of high-dose dexamethasone can also produce responses in refractory myeloma (13). In each of these regimens, unlike the present study, corticosteroids were given to patients either for the first time or in regimens with marked intensification of dosage and frequency of drug administration. In the present series all but one of the responding patients had previously been refractory to prednisone and virtually the same dose and schedule. Therefore, it is unlikely that the responses to hexamethylmelamine plus prednisone are due to prednisone alone. These data suggest that prednisone augments the effectiveness of hexamethylmelamine in multiple myeloma. There is precedence for this apparent synergy of corticosteroids with other agents in the treatment of multiple myeloma. A randomized study demonstrated that the addition of prednisone to high-dose intermittent melphalan therapy doubled the response rate in previously untreated patients with multiple myeloma (14). Furthermore, in the vincristine, doxorubicin, and dexamethosone regimen (13,15) vincristine and doxorubicin, two agents with only marginal single-agent activity in multiple myeloma (16,17), added significantly to the activity of high-dose dexamethasone in what could be a synergistic combination (13).

The treatment of multiple myeloma is hampered by the paucity of known active chemotherapeutic agents. It is important to recognize that drugs such as doxorubicin, vincristine, and hexamethylmelamine, which have marginal single-agent activity in this disease, may be useful when employed in potentially synergistic combinations. The combination of hexamethylmelamine and prednisone demonstrates this phenomenon, in that the activity of hexamethylmelamine in multiple myeloma appears to be dependent on the concomitant administration of corticosteroids.

REFERENCES

1. BENNETT JM, LENHARD RE, JR, EZDINLI E, ET AL. Chemotherapy of non-Hodgkin's lymphomas: Eastern Cooperative Oncology Group experience. Cancer Treat Rep 61:1079–1083, 1977.
2. BERGEVIN PR, TORMEY DC, and BLOM J. Clinical evaluation of hexamethylmelamine (NSC-13875). Cancer Chemother Rep 57: 51–58, 1973.
3. BORDEN EC, LARSON P, ANSFIELD FJ, ET AL. Hexamethylmelamine treatment of sarcomas and lymphomas. Med Pediatr Oncol 3:401–406, 1977.
4. LEGHA SS, SLAVIK M, and CARTER SK. Hexamethylmelamine. An evaluation of its role in the therapy of cancer. Cancer 38:27–35, 1976.
5. OMURA GA, BROUN GO, PAPPS J, ET AL. Phase II study of hexamethylmelamine in refractory Hodgkin's disease, other lymphomas, and chronic lymphocytic leukemia. Cancer Treat Rep 65:1027–1029, 1981.
6. WORZALLA JF, RAMIREZ G, and BRYAN GT. *N*-Demethylation of the antineoplastic agent hexamethylmelamine by rats and man. Cancer Res 33:2810–2815, 1973.
7. COHEN HJ. Hexamethylmelamine: a new agent effective in the treatment of refractory multiple myeloma. Blood 50(suppl 1):187, 1977.
8. OKEN MM, CREECH RH, TORMEY DC, ET AL. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649–655, 1982.
9. DURIE BGM, and SALMON SE. A clinical staging system for multiple myeloma. Cancer 36:842–854, 1975.
10. COHEN HJ, and BARTOLUCCI AA. Hexamethylmelamine and prednisone in the treatment of refractory multiple myeloma. Am J Clin Oncol 5:21–27, 1982.
11. SALMON SE, SHADDUCK RK, and SCHILLING A. Intermittent high-dose prednisone (NSC-10023) therapy for multiple myeloma. Cancer Chemother Rep 51:179–187, 1967.
12. ALEXANIAN R, YAP BS, and BODEY GP. Prednisone pulse therapy for refractory myeloma. Blood 62:572–577, 1983.
13. ALEXANIAN R, BARLOGIE B, and DIXON D. High-dose glucocorticoid treatment of resistant myeloma. Ann Intern Med 105:8–11, 1986.
14. ALEXANIAN R, BONNETT J, GEHAN E, ET AL. Combination chemotherapy for multiple myeloma. Cancer 30:382–389, 1972.
15. BARLOGIE B, SMITH L, and ALEXANIAN R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med 310:1353–1356, 1984.
16. JACKSON DV, CASE LD, POPE EK, ET AL. Single agent vincristine by infusion in multiple myeloma. J Clin Oncol 3:1508–1512, 1985.
17. ALBERTS DS, and SALMON SE. Adriamycin (NSC-123127) in the treatment of alkylator-resistant multiple myeloma: a pilot study. Cancer Chemother Rep 59:345–350, 1975.