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Methylprednisolone as Palliative Therapy for Female Terminal Cancer Patients

T. POPIELA,* RENATO LUCCHI,† FULVIO GIONGO‡
and the Methylprednisolone Female Preterminal Cancer Study Group

Abstract—*A total of* 173 *female terminal cancer patients were randomized to treatment with daily* 125 mg *infusions of methylprednisolone sodium succinate or a matching placebo for a period of* 8 *consecutive weeks. Data were collected relative to quality of life, investigator assessment of efficacy and cause and time of death within the* 8*-week treatment period.*

Significant improvement in quality of life was reported across the 8*-week follow-up period in the steriod group. Investigator global assessment of efficacy significantly favored the steroid-treatment patients. There were no significant differences between treatment groups with regard to overall mortality rates or time to death.*

The total number of reported adverse events did not differ significantly between treatment groups. However, significantly more steroid patients reported gastrointestinal and cardiovascular events. The severity and outcome of these events did not differ from the placebo patients.

The results of this study confirm previous reports of steroid efficacy in improving quality of life in terminal cancer patients. The absence of any untoward effect on mortality and the favorable safety profile support the use of methylprednisolone as palliative therapy for terminal cancer patients.

INTRODUCTION

THERE IS a recognized need for palliative therapy for patients with cancer who are in the terminal or advanced stages of their disease. Patients with terminal cancer are those whose disease has progressed to the stage where aggressive anticancer treatment is no longer indicated or effective. The life expectancy for such patients is generally estimated to be 3 months or less. In this clinical setting, therapeutic intervention should be palliative in nature and primarily designed to improve the diverse symptomatology which frequently accompanies this stage of cancer progression, namely: cachexia, nausea, vomiting, anxiety, sleeplessness, and pain. Drugs most frequently prescribed for these patients, narcotics and sedatives, may provide effective control of pain or anxiety, but have little or, perhaps, even an adverse effect on other quality-of-life parameters.

Corticosteriods have been considered for palliative therapy of terminal cancer since the early 1960s [1]. Several reports have been published which indicate that repeated corticosteroid doses of up to 600 mg/day over periods as long as 42 weeks [2] have produced consistent improvements in appetite and well-being [2, 4] while reducing pain and the need for analgesics [4, 5]. While there was initial speculation that steroid administration might actually increase the expected survival time for these patients, this has not proven to be true. In fact, one investigator has actually reported decreased survival time following a course of cortisone treatment [1].

As with studies examining the anticancer effects of chemotherapeutic regimens, controlled clinical trials of palliative therapy for these patients are difficult to perform and are therefore rare. Motivated by suggestions of efficacy from previous uncontrolled clinical trials, a double-blind, placebo-

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The Methylprednisolone Female Preterminal Cancer Study Group consisted of the following persons and institutions: The Upjohn Company (Kalamazoo, Michigan, U.S.A.), Study Coordinating Center: Dr J.M. Decoster, C.A. Metz, M.S., Dr G.B. Goris, D.L. Anderson, M.S., Dr A. Silva; Participating centers: University of Krakow, Poland: Professor T. Popiela; Ospedale Estense, Modena, Italy: Professor R. Lucchi; Ospedale L. Sacco, Milan, Italy: Professor F. Giongo; Ospedale Oncologico M. Ascoli, Palermo, Italy: Professor G. Paparopoli; Akademisch Ziekenhuis, Gent, Belgium: Dr J. Huys; St.Jozefkliniek A.Z., Oostende, Belgium: Dr J.P. Baeyens; Centro Regional de Oncologia, Sevilla, Spain: Dr. E. Murillo; Istituto di Oncólogia dell' Università, Messina, Italy: Professor S. D'Aquino; Ospedale Maggiore Bellaria, San Lazzaro di Savena, Italy: Professor M. Piazzi; Ospedale Niguarda-Ca' Granda, Milan, Italy: Professor E. Ghislandi; Ospedale Santa Maria, Terni, Italy: Professor A. Puxeddu; Instytut Onkologii, Warsaw, Poland: Dr J.A. Zborzil; Huize Vita Nove, Oss, Holland: Dr H.P. Deurenberg.
Author responsible for correspondence and to whom requests for reprints should be sent: Craig A. Metz, Project Manager, The Upjohn Company, Unit 9158-298-230, Kalamazoo, MI 49001, U.S.A.

controlled, clinical trial of methylprednisolone sodium succinate (MPSS) (SOLU-MEDROL®, The Upjohn Company) in terminal cancer patients was initiated in 1978. Treatment consisted of daily intravenous administration of 125 mg of MPSS or matching placebo for a period of 8 consecutive weeks. The results of this 403-patient study [6] indicated a significant improvement for MPSS-treated patients in pain, appetite, sense of well-being, vomiting, and other subjective evaluation instruments. The one distressing observation from this study was the significant decrease in survival time for female MPSS-treated patients. An exhaustive search for and analysis of potential contributing covariates failed to provide a reasonable explanation for this observation. Therefore, in 1984, a second study was initiated which was limited to female terminal cancer patients. The purpose of this study was to obtain additional data relative to total mortality rate and time to death for steroid and placebo-treated patients. A second goal was to confirm previous observations relative to improvement in quality of life following a prolonged course of steroid therapy.

METHODS AND MATERIALS

Inclusion/exclusion criteria

The inclusion/exclusion criteria for this study are presented in Table 1.

Investigational therapy

This was a randomized, prospective, double-blind, placebo-controlled, clinical trial. Patients were randomized to receive a daily 125 mg intravenous dose of MPSS or matching placebo for 56 consecutive days. Study medication was provided in blinded packages which contained vials of either placebo or MPSS as specified by a computer-generated randomization scheme.

Clinical evaluation

A patient history, physical examination, and informed consent were obtained at study admission. LASA scales were constructed in accordance with the technique described by Priestman and Baum [7] and completed by the patient at admission and weekly for the 8-week study medication period. The LASA scale, itself, consisted of patient ratings for pain, appetite, sense of well-being, nausea, sleep, weakness, anxiety, alertness, and vomiting. The patients marked a point on the 10-cm scale corresponding to their status at that point in time. These marks were converted to numerical scores on a 100-point scale. Body weight and information on the use of narcotic and non-narcotic analgesics, antinauseants, sedatives, and antibiotics was obtained at admission and weekly throughout the 8-week treatment period. Upon study completion, the physician was asked to give a global assessment

Table 1. *Inclusion/exclusion criteria*

Inclusion	Exclusion
1. Advanced, terminal cancer with pain, debility, nausea, cachexia, etc.	1. Previous study inclusion
2. Female	2. Concurrent participation in other experimental protocols
3. No further anticancer therapy anticipated	3. Concurrent corticosteroid therapy or corticosteroid therapy of greater than 2 weeks duration within 1 month of study enrollment
4. Minimum expected survival time of at least 2 months from study enrollment	4. Anticancer therapy within 2 weeks of study enrollment
5. Willing to consent to participate according to local custom	5. Pregnancy
	6. Active peptic ulcer or evidence of gastrointestinal bleeding
	7. Systemic fungal infection
	8. Active TB
	9. Uncontrolled diabetes mellitus
	10. Acute febrile illness
	11. Psychosis
	12. Abnormal mental status which could interfere with completion of subjective evaluations
	13. Neoplastic disease other than solid tumors
	14. Patients who would be unavailable for the entire 8-week follow-up period

of the efficacy of investigational therapy for each individual patient. The global assessment was made using a five-point scale consisting of the following responses with their relative point value: (1) excellent, (2) good, (3) fair, (4) poor, or (5) none. Medical events were recorded as they occurred and their relationship to therapy was determined. A death report specifying the date and cause of death was required for all patients who expired during the 8-week treatment period.

Statistical analysis

An 'intent-to-treat' analytical format was followed for this study. Once randomized, all patients and their respective data were included in the statistical analysis. Continuous variables were evaluated using analysis of variance (ANOVA) techniques [8]. To adjust for possible differences at baseline, the analysis was conducted on the change-from-baseline values at each time point. The model for ANOVA was the two-way interaction model, with both investigator and treatment considered as fixed effects. When a marginally significant investigator-by-treatment interaction was present ($P < 0.10$), the test for treatment effect was considered to be invalid. A one-way ANOVA for treatment effect was calculated for each investigator, and plots of the treatment effects by investigator were made. The investigator with the greatest deviation among treatments was excluded from the analysis and the two-way ANOVA model was run again. If no interaction was present, the test for treatment effect was obtained from this analysis.

Categorical variables were analyzed using the chi-square statistic in conjunction with the Cochran–Mantel–Haenszel chi-square used to control for investigator differences. In cases where there was a sparse distribution of responses in the frequency table, the categories were reduced to binary variables. A test for investigator-by-treatment interaction for the binary variables was conducted using the Breslow–Day test for homogeneity of the odds ratio.

Life table techniques [8] were used to calculate survival distribution estimates. The log-rank statistic, modified for censuring, was calculated to test the equality of the treatment groups over the survival distribution estimates. Patients who could not be followed until death were assigned censured values based on the last date they were known to be alive.

Comparability of the treatment groups at baseline was evaluated using the analysis of variance techniques for continuous variables and the chi-square test for homogeneity of categorical variables.

A P-value ≤ 0.05 was considered to be statistically significant. P-values > 0.05 but ≤ 0.10 were considered marginally significant and are subsequently referred to as trends.

RESULTS

Demographic data

A total of 173 patients were enrolled across the 13 international centers participating in this study. Since there was no study requirement for hospitalization, these patients represent a mixture of outpatients and inpatients. Eighty-five and 88 patients were randomized to treatment with MPSS and placebo, respectively. There were no significant differences between treatment groups with regard to age [64.9 (± 1.5) years MPSS; 65.8 (± 1.4) years placebo] or predicted survival time [3.4 (± 0.2) months MPSS; 3.5 (± 0.2) months placebo]. Approximately 96% of all patients were post-menopausal. Eighty-five per cent of the patients in each treatment group had primary gastrointestinal, breast or genitourinary cancers. Bone, liver, or lung were the most prevalent secondary tumor sites in both the MPSS (85%) and placebo (91%) groups. Only 29 patients (16 MPSS; 13 placebo) had no secondary tumor site. A grouping of 'other' secondary sites was developed for those metastases which did not fit into one of the three major categories (bone, liver, and lung). A total of 146 patients (70 MPSS; 76 placebo) had no major complicating illness other than their cancer. Major illnesses that were present (heart failure, respiratory failure, kidney disease) were evenly distributed between the treatment groups. Forty-four per cent of the steroid patients completed the entire 8-week treatment regimen versus a 57% completion rate for the placebo group (n.s.).

The primary reason for noncompletion of investigational therapy was death (38% MPSS; 30% placebo, n.s.).

Mortality

There were no significant differences between treatment groups with regard to overall mortality during the 8-week study follow-up period. The life-table analysis, which incorporates time to death, is displayed in Fig. 1. Although the steroid-treated patients died somewhat earlier than the placebo patients, there are no significant differences between treatments with regard to time to death. Further analysis of time to death by investigator revealed a significant investigator interaction at two of the 13 study centers. When the data from these two centers were removed from the life-table analysis, the total survival curves for the MPSS- and placebo-treated patients became nearly identical in appearance (Fig. 1). An analysis of time to death by primary tumor site did not produce any statistically significant differences between the two treatment groups.

Quality of life (LASA scales)

For purposes of standardization and analysis, LASA scores were converted in such a way that

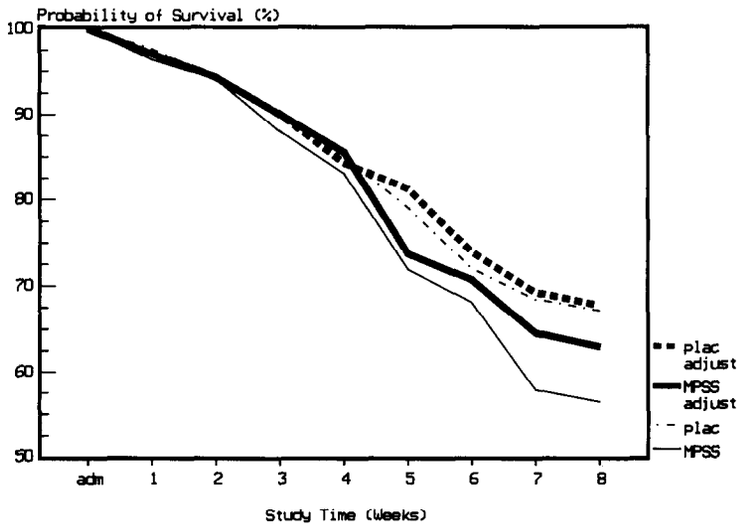

Fig. 1. Life table analysis (percentage probability of survival).

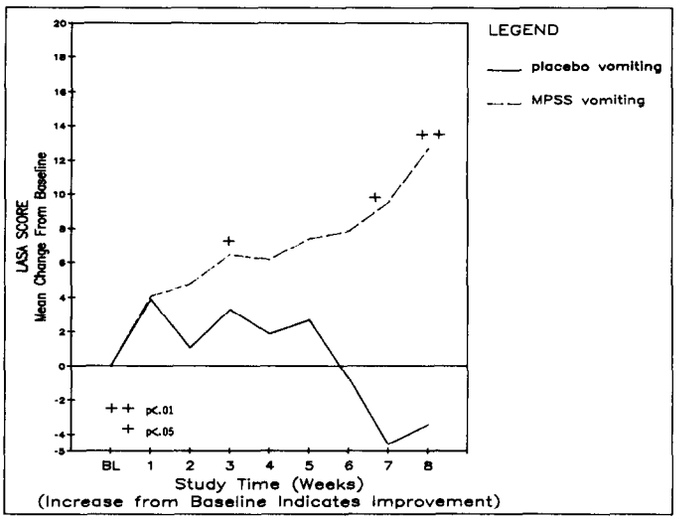

Fig. 2. Vomiting LASA scores (mean change from baseline).

higher scores always represented a better patient rating for that parameter. MPSS and placebo patients were comparable at admission with regard to all of the quality-of-life parameters with the exception of anxiety. At baseline, there was a trend towards greater anxiety in the steroid patients [39.2 (± 2.8) MPSS; 46.9 (± 3.2) placebo, $P = 0.08$]. There were no significant changes across time for pain or sleep. The steroid group experienced significantly greater mean change from baseline improvements in the feeling of weakness than the control group at follow-up week 1 [12.3 (± 2.4) ($n = 78$) MPSS; 2.84 (± 2.1) ($n = 85$) placebo, $P < 0.01$] and week 2 [13.8 (± 2.8) ($n = 74$) MPSS; 5.0 (± 3.0) ($n = 82$) placebo, $P < 0.05$]. Appetite (Fig. 2), nausea (Fig. 3), anxiety (Fig. 4), sense of well-being (Fig. 5), appetite (Table 2), and alertness (Table 3) showed consistent, often statistically significant, improvement across time in the MPSS-treated patients when compared with the placebo group.

To obtain an overall assessment of quality of life, the scores from all LASA categories were combined for each follow-up point and compared to admission. Combined scores for the steroid patients were significantly better than those of the placebo patients at all follow-up weeks except weeks 1 and 6 (Fig. 6).

On the five-point global evaluation of efficacy, 34% of the investigators rated steroid treatment as good or excellent compared with a 21% rating for the placebo patients. The mean rating for MPSS was also significantly better than placebo [3.11 (± 0.13) MPSS; 3.47 (± 0.12) placebo, $p < 0.05$].

Concomitant medications

There were no significant differences in narcotic analgesic usage between the two treatment groups at admission or any point during the study follow-

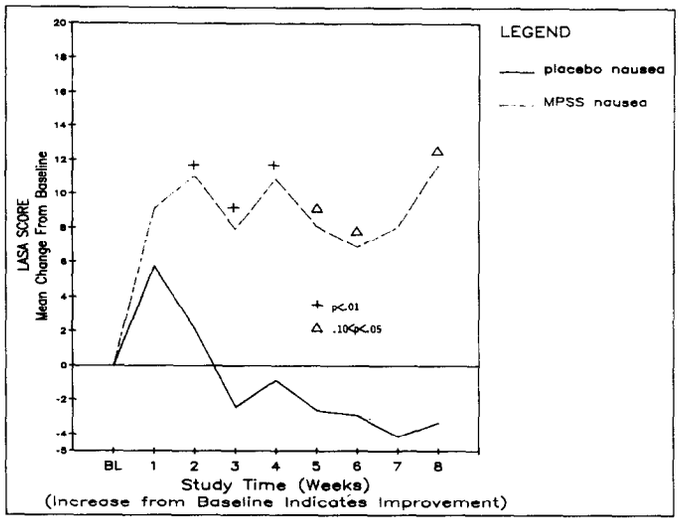

Fig. 3. Nausea LASA scores (mean change from baseline).

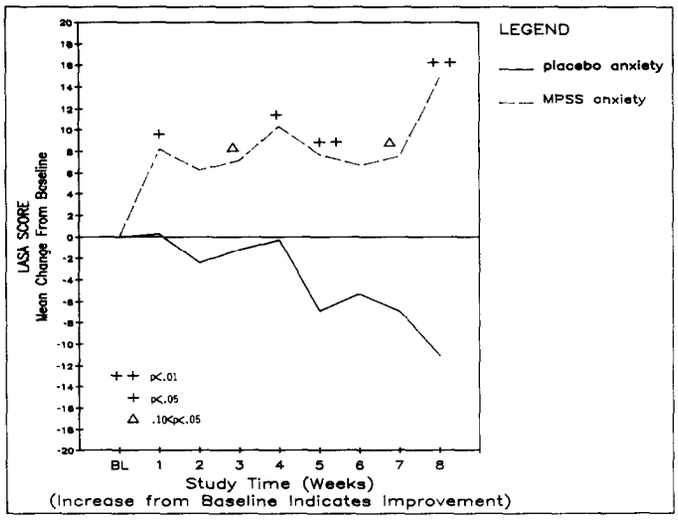

Fig. 4. Anxiety LASA scores (mean change from baseline).

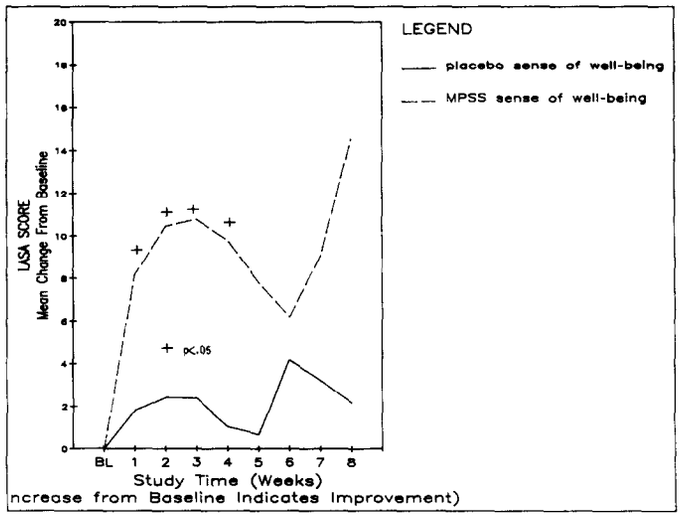

Fig. 5. Sense of well-being LASA scores (mean change from baseline).

Table 2. Appetite (mean change from baseline)

	MPSS	(Standard error)	(*n*)	Placebo	(Standard error)	(*n*)
Baseline	31.5	(±2.6)	(85)	28.8	(±2.5)	(88)
Week 1*	12.9	(±2.4)	(72)†	7.8	(±1.9)	(79)
Week 2*	17.1	(±3.4)	(66)‡	8.9	(±2.6)	(74)
Week 3	19.1	(±3.9)	(68)	11.6	(±2.8)	(76)
Week 4	21.3	(±4.4)	(62)	10.3	(±3.2)	(72)
Week 5	18.2	(±5.0)	(54)	10.9	(±3.6)	(64)
Week 6	21.3	(±5.3)	(49)	14.3	(±3.9)	(57)
Week 7	24.6	(±6.2)	(40)†	10.8	(±4.1)	(51)
Week 8*	23.1	(±7.9)	(28)	10.1	(±5.1)	(38)

*Data from one investigator excluded to remove treatment by investigator interaction.
‡$P \leq 0.05$.
†$0.5 < P \leq 0.10$.
Note: increase from baseline indicates improvement.

Table 3. Alertness (mean change from baseline)

	MPSS	(Standard error)	(*n*)	Placebo	(Standard error)	(*n*)
Baseline	59.6	(±3.2)	(85)	53.6	(±3.2)	(88)
Week 1	5.4	(±2.5)	(78)	−0.6	(±2.6)	(85)
Week 2	3.9	(±3.0)	(74)	0.9	(±3.1)	(82)
Week 3	7.8	(±2.9)	(67)*	−1.5	(±2.5)	(76)
Week 4	5.0	(±3.1)	(62)	−0.7	(±3.1)	(72)
Week 5	2.5	(±3.6)	(54)†	−5.8	(±3.5)	(64)
Week 6	4.2	(±4.5)	(49)	−0.7	(±3.6)	(57)
Week 7	5.8	(±4.6)	(40)	−1.6	(±4.2)	(51)
Week 8	14.8	(±4.6)	(35)*	−4.1	(±4.7)	(44)

*$P \leq 0.05$.
†$0.5 < P \leq 0.10$.
Note: increase from baseline indicates improvement.

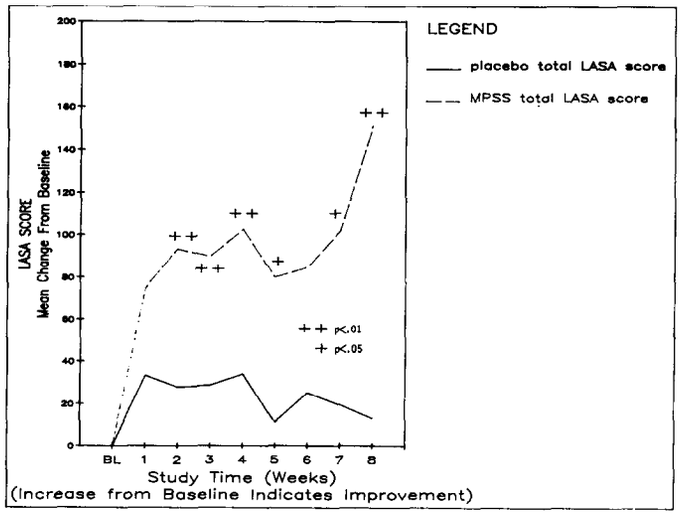

Fig. 6. Total LASA score (mean change from baseline).

up period. The number of patients taking non-narcotic analgesics was similar to admission. Trends towards fewer steroid patients initiating non-narcotic analgesic therapy and more steroid patients discontinuing non-narcotic analgesic treatment were present at weeks 5 and 6. These trends became significant at week 7 with 9.7% of the steroid patients starting non-narcotic analgesics versus 17% of the patients in the placebo group ($P < 0.05$).

The frequency of antinauseant administration did not differ within the two treatment groups at any point during the study. At weeks 7 and 8, 3/41 and 4/37 steroid patients began taking sedatives versus 0/53 and 0/49 patients in the placebo group during the same time frame. These differences were significant ($P < 0.05$).

Complications of investigational therapy

Reported infectious complications were comparable between treatment groups (11.8% MPSS; 14.8% placebo). Consistent with this observation, antibiotic usage was also similar at admission and at all subsequent follow-up points. There were no significant differences across time with regard to weight, hemoglobin, or hematocrit.

A combined total of 145 medical events were reported by 54 (63.5%) MPSS patients and 47 (53.4%) placebo patients. These events were classified as cardiovascular, gastrointestinal, shock/respiratory failure, infection/inflammation, metabolic, unrelated to investigational therapy, or other. There were significantly more gastrointestinal (9/85, 10.6% MPSS; 2/88, 2.2% placebo, $P < 0.05$) and cardiovascular (7/85, 8.2% MPSS; 1/88, 1.1% placebo, $P < 0.05$) side-effects reported in the steroid group. Although significantly more of the adverse events were felt to be either related or probably related to investigational therapy (21% MPSS; 1% placebo, $P < 0.05$), there were no differences between treatments with regard to the severity of the event, as assessed by the investigator, or its ultimate outcome.

DISCUSSION

Clinical trials, both controlled [1, 4, 6] and uncontrolled [2, 3, 5] have suggested that extended administration of corticosteroids to terminal cancer patients has a beneficial effect on quality of life. We have confirmed these findings in the present randomized, double-blind, placebo-controlled study by demonstrating significant improvement in appetite, sickness, nausea, weakness, alertness, anxiety, vomiting, and total LASA score following an 8-week intravenous course of 125 mg of MPSS daily. The patient observations of improved quality of life were further substantiated by the clinical investigators who reported significantly better ratings for the steroid-treated patients in their global assessments of efficacy.

Two previous studies have reported decreased survival times in terminal cancer patients receiving corticosteroids [1, 6]. Although survival time from the MPSS patients in the current study was shorter than their placebo counterparts, the differences between the two treatment groups did not approach statistical significance and were the principal result of investigator interaction at two of the 13 study centers. Infectious complications related to steroid administration were not evident in this study. While there were significantly more reports of gastrointestinal or cardiovascular events in the steroid group, these events did not differ from the placebo group with regard to severity or final outcome.

There is a recognized need for palliative therapy for cancer patients in the terminal stages of their disease. Therapeutic management with drugs (such as narcotics and sedatives) may provide effective control for pain, but have little or, perhaps, even an adverse effect on nausea, vomiting, alertness, appetite, and the patient's ability to relate to family members. The results of this study have demonstrated that treatment with MPSS may be an important adjunct to improving the quality of life in this patient population.

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