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Effect of Methylprednisolone Sodium Succinate on Quality of Life in Preterminal Cancer Patients: A Placebo-controlled, Multicenter Study

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Abstract—*The effectiveness of an 8-week, 125 mg/day intravenous course of methylprednisolone sodium succinate (MPSS) for improving quality of life in patients with preterminal cancer was investigated in a double-blind, placebo-controlled, multicenter study. Quality of life was assessed using the Nurses' Observational Scale for Inpatient Evaluation (NOSIE), the Linear Analog Self-Assessment Scale (LASA), and the Physicians' Global Evaluation. A total of 403 patients were enrolled: 207 were treated with MPSS and 196 were treated with placebo. MPSS was significantly more effective than placebo in improving quality of life as judged by the changes from baseline in the NOSIE and LASA total scores. ($P < 0.05$) and by the Physicians' Global Evaluation ($P < 0.001$). The mortality rate was similar between MPSS-treated males (40.2%), placebo-treated males (35.5%), and MPSS-treated females (40.0%). However, the mortality rate of 27.7% for female placebo-treated females was significantly lower than for their MPSS-treated counterparts. The reason for lower mortality among placebo-treated females is unknown and warrants further study.*

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INTRODUCTION

SEVERAL REPORTS in the literature have suggested that corticosteroids are useful for improving symptoms, such as anorexia and lethargy, in terminally ill cancer patients, thereby improving the quality of their lives in the final stages of their illnesses [1–3]. However, the lack of placebo-control groups and variations in the symptoms that were assessed make interpretation of these reports difficult.

In 1974, Moertel *et al.* [4] showed, in a double-blind, placebo-controlled study, that low-dose, oral treatment with dexamethasone was effective in improving appetite and in enhancing feelings of well-being in patients with far-advanced gastrointestinal cancer but that dexamethasone treatment was not effective in promoting weight gain or in improving performance status. Survival rates in this palliative therapy study were similar between the dexamethasone- and placebo-treated patients. In another placebo-controlled study of patients with inoperable bronchogenic carcinoma, Wolf *et al.* [5] showed that survival time was significantly shorter when cortisone was used as a component of the anticancer treatment regimen.

Several oncologists have reported favorable results in cancer patients treated with methylprednisolone sodium succinate (MPSS) (SOLU-

MEDROL® Sterile Powder, The Upjohn Company). In one uncontrolled study, improvement in appetite, weight gain, a reduction in analgesic agent use, and a euphoric effect were noted in patients with various cancers who were treated intravenously (i.v.) with MPSS in doses ranging from 80 to 120 mg daily [6]. Similar observations were reported in another study in which daily doses of up to 200 mg of MPSS were used [7].

The purpose of this double-blind, placebo-controlled, multi-center study was to evaluate the effectiveness of an 8-week course of MPSS, administered in daily doses of 125 mg i.v., for improving quality of life in patients with preterminal cancer. A secondary purpose of this study was to determine the effects of MPSS treatment on short-term survival.

PATIENTS AND METHODS

Study design

Patients of either sex and of any age with advanced, preterminal carcinoma were eligible for inclusion in the study if they suffered pain, debility, cachexia, anorexia, or other signs of advanced disseminated disease, were no longer candidates for aggressive anticancer therapy, and were expected to survive for at least 2 months. Patients who were suffering from acute febrile illness, who were psychotic, who had an active peptic ulcer, and who were pregnant were excluded from the study as were those who had had major surgery within 2 weeks prior to consideration for the study; those who were receiving corticosteroid therapy or who had finished corticosteroid therapy within 1 month prior to consideration for the study; and those who were mentally deficient or disturbed. Informed consent was obtained from each patient in accordance with the Declaration of Helsinki.

At study entry, patients were randomized in a double-blind fashion to receive daily i.v. treatment with MPSS 125 mg or with placebo; mannitol (88.8 mg) was the principal component of the placebo. Study medication was provided in blinded packages which contained vials of either MPSS or placebo as specified by a computer-generated randomization scheme. The identity of the investigational therapy was not known by the investigator, his staff, or the patient. Patients were treated for as long as they lived or for a maximum of 8 weeks. Body weight was determined weekly, and serum calcuim, potassium and hemoglobin levels were determined every other week.

Quality of life was assessed at study entry and weekly using the Nurses' Observation Scale for Inpatient Evaluation (NOSIE) [18]. The NOSIE scale comprised 21 questions. A nurse scored each question, based on the patient's behavior during the previous 3-day period, on a five-point scale ranging from 'never' to 'always'. Five factor scores (social competence, social interest, irritability, retardation, e.g. difficulty completing simple tasks, sluggish, and depression) and a total score were derived; the total score was calculated as follows:

$$\text{Total score} = 50 + \text{social competence} + \text{social interest} - \text{irritability} - \text{retardation} - \text{depression}.$$

An increase from baseline in the NOSIE total score was indicative of improvement with treatment.

A second instrument for assessment of quality of life, the Linear Analogue Self-Assessment scale (LASA) [9], was also employed in this clinical trial. The LASA scale comprised 10 questions, which inquired about pain, appetite, well-being, nausea, sleepiness, weakness, drowsiness, anxiety, mood, or vomiting. Patients scored each question on a 10-point scale ranging from 'worst' to 'best'. Each individual question and the LASA total score were evaluated; an increase from baseline in the LASA total or individual question scores was indicative of improvement with treatment.

Overall drug effect was assessed at the end of treatment using an instrument developed specifically for this study, the Physicians' Global Evaluation Scale. The global assessment of efficacy was made using a five-point scale consisting of the following responses with their respective point values: (1) excellent, (2) good, (3) fair, (4) poor, or (5) none.

Except for additional corticosteroids, patients received whatever treatment their physicians deemed necessary. Concurrent medication was recorded on forms provided to the investigator.

Data analysis

An intent-to-treat format was followed for the statistical analysis of this study. Once randomized, all available patient data was used for each evaluation interval. For NOSIE and LASA scales, change from baseline scores were used in the statistical analysis. Interval, ordinal, and continuous data were analyzed using the t-test [10]. Binominal data and nominal data were analyzed by Fisher's exact test or by the extension thereof [11]. The life-table survivorship curves were analyzed by the z-test [12] using the life-table procedures described by Cutler and Ederer [13] and the standard error given by Greenwald [14]. Statistically significant differences were defined to be those with a P-value < 0.05. Marginally significant differences were defined to be those with a P-value ≥ 0.05 but ≤ 0.10.

RESULTS

A total of 403 patients were enrolled in the study by 26 investigators in Belgium, Holland, Italy,

Poland, Spain, and Yugoslavia; 207 were randomized to receive treatment with MPSS, and 196 were randomized to receive treatment with placebo. Although there was no specific study requirement for hospitalization, most of the patients enrolled in this clinical trial were inpatients. The treatment groups were comparable in age, sex, life expectancy (Table 1), and in primary tumor site prior to treatment. Among male patients, the major tumor sites were the lung (38.8%), stomach (12.8%), buccal cavity and pharnyx (11.2%), prostate (7.1%), and rectum and rectosigmoid junction (5.1%); among female patients, the major tumor sites were the breast (34.8%), stomach (10.1%), large intestine (11.1%), cervix uteri (7.7%), lung (5.3%), and rectum and rectosigmoid junction (5.3%).

At baseline, there were no significant differences between treatment groups with regard to drugs which might affect quality of life parameters (e.g. narcotic and non-narcotic analgesics and sedatives/tranquilizers) or other supportive therapy such as antibiotics and cardiovascular drugs. Subsequent to baseline, there were no significant differences in concomitant therapy between treatment groups.

Ninety-four (45.4%) MPSS-treated and 104 (53.1%) placebo-treated patients completed the 8-week course of treatment. The remaining patients either dropped out of the study for various reasons (30 MPSS-treated and 33 placebo-treated patients) or died (83 MPSS-treated and 59 placebo-treated) prior to completing 8 weeks of treatment. The number of patients remaining in the study at the various follow-up evaluations is presented in Table 2.

The mean NOSIE total score (mean ± S.D. 61.8 ± 12.5 in the MPSS-treated group and 61.0 ± 13.5 in the placebo-treated group) and mean factor scores were comparable between treatment groups at baseline. MPSS was significantly more effective ($P < 0.05$) than placebo in improving the NOSIE total score at all but week 6 of treatment; these results are illustrated in Fig. 1, which shows the mean change from baseline in the NOSIE total score at each week of treatment. Similar results were observed for two of the five factor scores: MPSS was significantly more effective ($P < 0.05$) than placebo in improving the social interest factor score at each follow-up evaluation and in improving the retardation factor score at all but week 1 of treatment. There were no significant differences between treatment groups in the social competance, irritability, or depression factor scores at any time during the study.

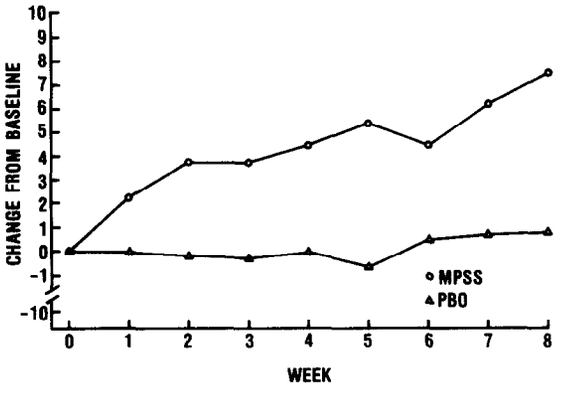
Mean LASA total scores were also comparable between treatment groups at baseline (mean ± S.D. 51.4 ± 17.2 in the MPSS-treated group and 50.0 ± 16.4 in the placebo-treated group) as were the mean scores for the individual LASA questions. At each weekly follow-up evaluation, MPSS produced significantly more improvement than placebo in the LASA total score and in the pain, appetite, vomiting, and well-being scores ($P < 0.05$). There were no differences between treatment groups in the remaining six individual LASA question scores

Table 1. Characteristics of study population at study entry

	MPSS $n = 207$	Placebo $n = 196$
Age (years)		
mean	62.4	63.0
range	16–87	37–91
Sex		
male	97 (46.8%)	99 (50.5%)
female	110 (53.1%)	97 (49.4%)
Life expectancy		
≤2 months	31 (15%)	34 (17.3%)
>2 but <3 months	94 (45.4%)	90 (45.9%)
≥3 months	73 (35.3%)	67 (34.2%)
not reported	9 (4.3%)	5 (2.6%)

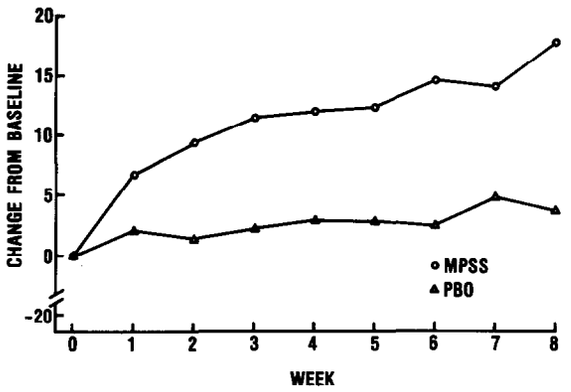
Table 2. Number of patients completing specified number of weeks of investigational therapy

Week	Total	SOLU-MEDROL®	Placebo
0	403	207	196
1	396	205	191
2	364	188	176
3	330	170	160
4	297	149	148
5	265	132	133
6	234	119	115
7	220	108	112
8	150	70	80



*Increase from baseline indicates improvement with treatment.

*Fig. 1. Mean change from baseline in NOSIE total score.**



*Increase from baseline indicates improvement with treatment.

*Fig. 2. Mean change from baseline in LASA total score.**

at any time during the study. The mean change from baseline in the LASA total score is illustrated in Fig. 2.

In the physicians' judgements, MPSS was significantly more effective than placebo in improving the quality of life in preterminal cancer patients ($P < 0.001$). Physicians rated the therapeutic effect of MPSS as good to excellent for 42% of the patients, fair for 27% of the patients, and poor for 34.8% of the patients. In contrast, they rated the therapeutic effect of placebo as good to excellent for 21.4% of the patients, fair for 21.4% of the patients, and poor for 50.5% of the patients. The Physicians' Global Evaluation was not completed for the remaining 1.5% of MPSS-treated and 1.1% of placebo-treated patients.

Mortality rate was similar between MPSS-treated males (40.2%), placebo-treated males (35.5%), and MPSS-treated females (40.0%) (Fig. 3). However, the mortality rate of 27.7% for female placebo-treated females was significantly lower than for their MPSS-treated counterparts. Cumulative survival curves (Fig. 4), which were derived from life table survivorship rates, showed that survival rate was significantly lower for MPSS-treated than for placebo-treated females at weeks 7 and 8 ($P < 0.05$ and $P < 0.01$, respectively).

Side-effects were reported by significantly more MPSS-treated (38.2%) than placebo-treated (28.1%) patients ($P < 0.05$). The most commonly reported side-effects were vomiting (three MPSS-treated and seven placebo-treated patients); hypocalcemia (six MPSS-treated and three placebo-treated patients); anemia (one MPSS-treated and seven placebo-treated patients) and hyperglycemia (eight MPSS-treated and no placebo-treated patients). Eleven patients (10 MPSS-treated and one placebo-treated) dropped out of the study due to side-effects. Among the side-effects reported by the MPSS-treated patients who dropped out of the study were stomach pain (three patients); hypotension (two patients); hyperglycemia (one patient); hypoalbuminemia (one patient); hematemesis (one patient); and gastrointestinal bleeding (one patient).

There were no statistically significant differences between treatment groups in body weight, serum

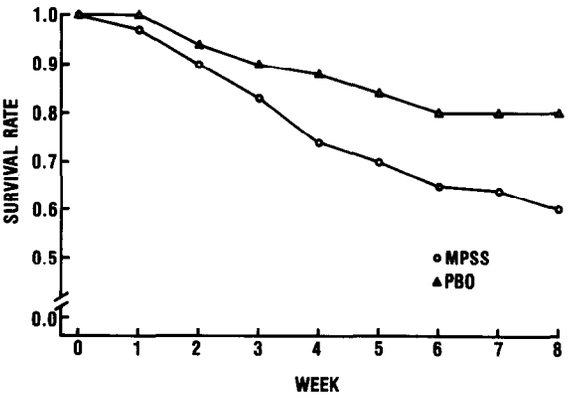


Fig. 4. Survival rate for female patients.

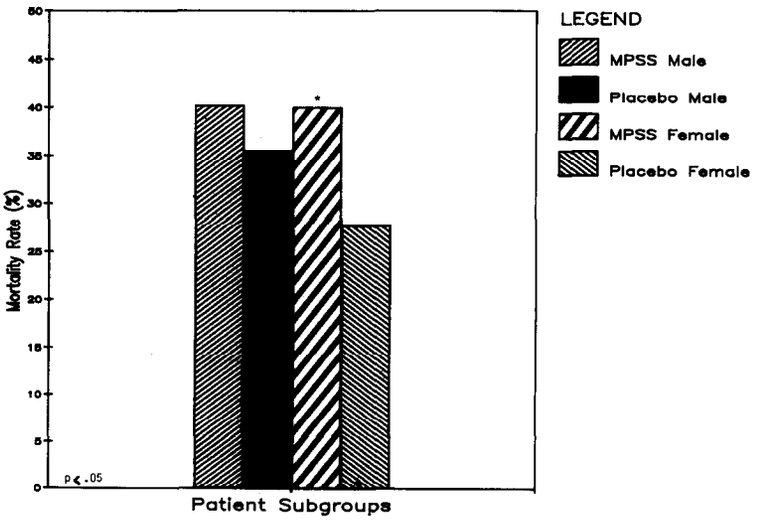


Fig. 3. Mortality rate by treatment group and sex.

calcium, or potassium levels at baseline or at any follow-up evaluation. Although statistically significant differences were noted in hemoglobin concentration at weeks 2, 4, and 6, these differences were of a magnitude of <0.65 g/100 ml and were not considered clinically important.

DISCUSSION

The effectiveness of MPSS for improving quality of life in patients with preterminal cancer was investigated in this double-blind, placebo-controlled, multicenter study. Intravenous administration of 125 mg of MPSS daily for up to 8 weeks resulted in a significant improvement in quality of life as judged by the mean change from baseline in total scores for the observer-rated NOSIE and patient-rated LASA scales. Further support for the efficacy of MPSS in improving quality of life in preterminal cancer patients was obtained from the NOSIE factor and LASA individual question scores: MPSS was significantly more effective than placebo in improving the NOSIE social interest and retardation factor scores and in improving the LASA pain, appetite, vomiting, and well-being scores. Lastly, the Physicians' Global Evaluation provided additional evidence of the efficacy of MPSS in the treatment of preterminal cancer patients. Physicians rate the therapeutic effect of MPSS as good to excellent for 42% of the patients and as fair for 27% of the patients. In contrast, they rated the therapeutic effect of placebo as good to excellent for 21.4% of the patients and as fair for 21.4% of the patients.

Patients with terminal cancer present a challenge to the attending physician. Pain, metabolic derangements, nausea and vomiting, and emotional lability are but some of the possible therapeutic needs of this patient population. Furthermore, even palliative therapy in the form of narcotic analgesics, sedatives, and antiemetics is associated with its own inherent adverse effects. The medical consequences of corticosteroid therapy, particularly in high-dose, long-term situations, are well known. In the present study, 125 mg of MPSS given daily for a 56-day treatment period resulted in predominantly benign side-effects reports which occurred at a frequency of less than 5%. However, the main concern related to the potential for adverse effects in this study was the observation of a significant, though inexplicable, decrease in survival time for steroid-treated female patients. Although other studies evaluating corticosteroids as palliative therapy for terminal cancer have failed to confirm this observation, further examination of this issue in a subsequent clinical trial is indicated.

In considering palliative therapy of terminal cancer, the physician must make a risk-to-benefit assessment for each drug under consideration. The beneficial effect on quality of life combined with an acceptable safety profile for MPSS in this study indicates that MPSS should be considered as a viable therapeutic alternative for palliative therapy of terminal cancer.

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