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Anti-inflammatory Treatment May Prolong Survival in Undernourished Patients with Metastatic Solid Tumors[1]

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ABSTRACT

Eicosanoids may be important factors for tumor cell proliferation, metastatic formation, and development of cancer cachexia. The present study has evaluated the effect of anti-inflammatory treatment on tumor progression in clinical cancer. Patients (n = 135) with insidious or overt malnutrition due to generalized malignancy (various kinds of solid tumors) and an expected survival of more than 6 months were randomized by a computer-based algorithm to receive placebo, prednisolone (10 mg twice daily), or indomethacin (50 mg twice daily) p.o. until death. Patient groups were stratified in the randomization procedure for sex, tumor type, stage, nutritional state, and previous tumor treatment, and biochemical, physiological, and some functional variables (Karnowsky index, fatigue and pain score). A majority of these variables was then registered during the follow-up. Indomethacin and prednisolone treatment maintained Karnowsky index, while placebo-treated patients experienced a decreased index. Indomethacin-treated patients suffered less pain and consumed less additional analgetics compared to the other patient groups. Indomethacin prolonged mean survival compared to placebo-treated patients from 250 ± 28 days to 510 ± 28 days ($P < 0.05$). Survival analysis on observations from all patients treated with either indomethacin or prednisolone demonstrated a significantly prolonged survival by anti-inflammatory treatment compared to placebo treatment (log rank, $P < 0.03$). The results suggest that not only may prostaglandin synthesis inhibition offer palliative support to patients with solid advanced cancer, but it may also impact on pathways that ultimately determine outcome.

INTRODUCTION

Tumor cell proliferation, metastatic formation, and tumor-host deterioration are mediated by complex interactions between cytokines, growth factors, and classic hormones (1–3). Eicosanoids are also potentially important factors in the cascades that determine the tuned balance between growth arrest and tumor progression in both experimental and clinical cancer (4). Cytokines as interleukin 1, tumor necrosis factor, interleukin 6, γ-interferon, and perhaps additional factors are confirmed as significant mediators behind cancer cachexia (5, 6). It is also possible that eicosanoids may play a significant role in carcinogenesis (7). Animal studies in our laboratory have demonstrated that inhibition of prostaglandin synthesis attenuated tumor progression and reduced cancer cachexia to the same extent as inhibition with monospecific antibodies to cytokines (5). One possible explanation for this observation may be that second messengers to cytokines and growth factors sometimes depend on signal transduction by eicosanoids. If so, prostaglandin interventions should have significant effects on outcome and progression of cancer disease. Eicosanoids are not stored but are synthesized on demand. Therefore, inhibitors of the various oxygenases and peroxide-metabolizing enzymes have instantaneous effects on steady-state eicosanoid levels. This would represent an ideal premise for drug interventions to control malignant growth and tumor-host effects. In support of this conclusion, epidemiological evidence has been presented that patients on long-term aspirin treatment have a lower incidence of colon carcinoma (8, 9), and that patients on anti-inflammatory treatment due to rheumatoid arthritis have a lower risk to develop solid tumors (10). Our own studies have demonstrated that indomethacin treatment to tumor-bearing rodents prolonged survival and was even curative in some groups of tumor-bearing rats (11, 12). Controlled clinical studies have also confirmed that acute and short-term glucocorticoid treatment is a significant tool for palliation of acute and progressive symptoms due to growing tumors in patients (13, 14). All of this information made it interesting to test the hypothesis of whether long-term treatment with anti-inflammatory drugs would benefit patients suffering from solid and generalized tumors. Therefore, the aim of this study was to evaluate whether anti-inflammatory treatment by either indomethacin or prednisolone could attenuate the long-term progression of the disease in patients with generalized solid tumors.

MATERIALS AND METHODS

Patients. One hundred thirty-five patients were randomized at the Department of Surgery, Sahlgrenska Hospital, for treatment with indomethacin (50 mg x 2), prednisolone (10 mg x 2) or placebo. All patients were blinded for their treatment. Inclusion criteria were insidious or ongoing weight loss due to generalized malignant disease with a solid tumor type. No other efficient or established tumor treatment would be available to the patient and the most recent tumor therapy must have been completed beyond 6 months prior to starting our treatment. The expected survival was estimated to be more than 6 months. Exclusion criteria were: recent or present treatment with anti-inflammatory drugs, kidney function impairment with serum creatinine above 175 μmol/liter, body temperature or relapsing fever above 37.5°C, or cholestasis with serum bilirubin levels above 60 μmol/liter, (<21 μmol/liter is normal).

Randomization and Measurements before Treatment. All patients were randomized to treatment by a computer-based algorithm as described by Pocock and Simon (15), stratifying for tumor type, tumor stage, earlier tumor treatment (surgery, chemotherapy, radiotherapy), expected survival in months, age, sex, nutritional state (body weight, weight loss, serum albumin concentration, arm muscle circumference, triceps skinfold, and resting energy expenditure) (16), liver function tests (serum bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatases), serum creatinine, blood hemoglobin concentration, erythrocyte sedimentation rate, the Karnowsky index (describing performance status in activities of daily living) (17), and previous intake of analgetics.

Follow-up Measurements. Physiological variables included heart rate, systolic and diastolic blood pressure, body temperature, and respiratory frequency. Nutritional state variables, fatigue and pain sensation, use of analgetics, handgrip strength, and the Karnowsky index were also assessed during follow-up. Blood chemistry included hemoglobin concentration, WBC count, thrombocyte count, erythrocyte sedimentation rate, C-reactive protein, plasma protein concentration, serum albumin and the thyroid state (T4, free T4, T3, free T3, rT3, thyroid-stimulating hormone), plasma electrolytes, serum creatinine, and liver function tests.

Energy expenditure was measured by indirect calorimetry (Deltratrac; Datex, Helsinki, Finland) during resting conditions in the morning (18).

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Triceps skinfold and arm muscle circumference were measured by a specially trained nurse (16). Heart rate, systolic and diastolic blood pressure, body temperature, body weight, and respiratory frequency were measured according to routine clinical procedures. Fatigue and pain sensation were estimated by a specially trained nurse according to a visual analogue scale technique (19). The handgrip strength was assessed as described elsewhere (20) and the overall function ability of a patient (Karnowsky index) was classified by a nurse. All of these variables and measurements were determined at a 3-month interval until the patient died or the study was closed. All patients were informed prior to randomization by one of us. No patient refused to take part in the study. Each patient received a list of analgetics which would be appropriate to use in case of pain treatment not to interfere with the drugs under test. A group of nurses remained in continuous contact with all patients and their families to assist or respond to questions concerning the study protocol. The study was approved by the Committé for Ethics at The Medical Faculty, University of Göteborg.

Study Design and Statistics. The study was planned to test treatment effects on functional variables and nutritional state as the primary variables, and survival, if practically possible, as a secondary achievement. A two-sided significance level of 0.05 and a power of 0.90 should require around 60 randomized patients to determine a 25% improvement in function and nutritional state, while a similar significance and power required approximately 250 randomized patients to detect a 40–50% improvement in survival, based on a 50–60% mortality per year in the control group. According to preliminary estimations it was judged that the study should take 4–5 years to complete. Therefore, it was decided that the first evaluation should be done when one-half of the patients (more than 130) had been included. However, since both palliation and survival appeared improved in the treatment groups compared to placebo, we decided to interrupt the study and report the results. The justification for this decision was that indomethacin treatment is practically witout any side effects when given to cancer patients. Both indomethacin and prednisolone were considered effective anti-inflammatory drugs based on a large clinical documentation. Therefore, it was also included in the protocol to evaluate the results in the placebo group *versus* the entire groups of patients treated with anti-inflammatory drugs such as indomethacin and prednisolone. Comparisons among patient groups were made by one-factor analysis of variance with or without repeated measures (Super ANOVA; Abacus Concepts, Inc.) including a *post hoc* test (Fisher PLSD test) for determination of statistical differences between specified groups. Differences in survival were tested by the log-rank survival analysis in the SAS statistical package software.

RESULTS

Before Treatment

Randomization. Tumor type, tumor stage, earlier tumor treatment, and expected survival became well balanced among the three groups, and no significant differences were found in these respects (Table 1). The distributions of sex, age, body weight, nutritional state, blood chemistry, liver and kidney function tests, and the Karnowsky index were also similar without any significant difference among the patient groups (Table 2).

Follow-up and Outcome

Biochemical, Physiological, and Functional Variables. Placebo-treated patients had a significantly higher overall pulse rate during the follow-up period, while additional variables (blood pressure, body temperature, respiratory frequency) were not different among the groups. Indomethacin-treated patients had a significantly lower pain score, which was reflected by a reduced consumption of additional analgetics. The handgrip strength was significantly highest in the prednisolone group, while the Karnowsky index became significantly lower in the placebo group compared to both prednisolone- and indomethacin-treated patients (Table 3). Body weight and arm muscle circumference were significantly higher in prednisolone-treated patients (Table 4).

WBC count, thyroid-stimulating hormone, and some liver function tests (serum bilirubin, alanine aminotransferase) differed among the groups during follow-up, but these differences seemed of less clinical importance (Table 5).

Survival

Survival distribution among the various treatment groups differed with borderline significance when all the three groups were compared simultaneously against each other ($P < 0.07$) (Fig. 1). Indomethacin-treated patients had a significantly prolonged survival compared to placebo-treated patients ($P < 0.05$). Pooled observations from patients on anti-inflammatory treatment revealed a significantly prolonged survival compared to placebo-treated patients ($P < 0.03$, 274 ± 28 *versus* 505 ± 65 days) (Fig. 2).

DISCUSSION

Progress to improve treatment efficacy of generalized cancer disease due to solid tumors has been less rewarding during the past decades, although modern chemotherapeutical drugs have appeared that are more potent and less toxic. Therfore, it is of interest to consider alternative treatment and palliative options to traditional treatment regimens (2). The hypothesis under test was formulated based on a large body of information that eicosanoids may be important regulatory factors for tumor cell proliferation and tumor-host interactions in experimental systems. Prostaglandin synthesis intervention caused a dramatic and highly reproducible reduced cachexia and prolonged survival in tumor-bearing rodents, irrespective of whether indomethacin was introduced early or late during disease progression (11, 12). This achievment is usually not typical for other therapeutical agencies with tumorostatic characteristics. Thus, most regimens reported in the literature are most effective when introduced early, simultaneously, or even before tumor cells are inoculated. The unusual characteristic of indomethacin to prolong survival in tumor-bearing mice when introduced late in disease caused us to evaluate whether some of its beneficial effects could be observed in treatment of cancer patients who had little or no further therapy to rely on for treatment of a generalized and progressive malignancy. In addition, recent research has emphazised a possible role for eicosanoids as

Table 1 *Tumor type, stage, earlier treatments, and expected survival*

	Placebo[a]	Prednisolone [a]	Indomethacin[a]	ANOVA[b]
Tumor type				
Liver, pancreas	16	15	13	NS
Colon, rectum	10	8	12	NS
Gastric	6	4	8	NS
Oesophagus	5	7	3	NS
Melanoma	1	5	1	NS
Breast	1	1	1	NS
Head and neck	0	1	2	NS
Miscellaneous	6	4	5	NS
Tumor stage				
Local spread	11	12	16	NS
Liver metastasis	14	13	14	NS
Pulmonary metastasis	2	5	2	NS
Peritoneal metastasis	2	1	4	NS
Skeletal metastasis	0	1	0	NS
Earlier treatment				
Operation only	27	26	26	NS
Radiotherapy	0	0	1	NS
Chemotherapy	0	1	0	NS
Immune therapy	0	1	0	NS
More than one of above	5	4	5	NS
No earlier treatment	12	13	13	NS
Expected survival				
6 months	29	29	26	NS
6 to 12 months	14	12	16	NS
More than 12 months	2	4	3	NS

[a] Number of patients.
[b] ANOVA, analysis of variance; NS not significant.

Table 2 *Measurements before treatment and used in stratification*

	Placebo	Prednisolone	Indomethacin	ANOVA[a]
Male/female	28/17	29/16	29/16	NS
Mean age	66.00 ± 1.50[b]	66.00 ± 1.50	69.00 ± 1.50	NS
Body weight (kg)	65.50 ± 2.10	68.20 ± 2.00	66.00 ± 1.80	NS
Pretreatment weight loss (%)	10.40 ± 1.30	9.70 ± 1.30	9.30 ± 1.20	NS
Arm circumference (cm)	26.70 ± 0.50	27.00 ± 0.60	26.10 ± 0.70	NS
TSF (mm)	10.20 ± 0.70	11.80 ± 0.90	12.00 ± 0.80	NS
AMC	23.50 ± 0.50	23.30±0.60	22.30 ± 0.70	NS
REE/kg/day	24.50 ± 0.50	24.20 ± 0.60	24.40 ± 0.50	NS
Karnofsky index	76.00 ± 3.00	77.00 ± 4.00	74.00 ± 3.00	NS
Hemoglobin concentration (g/liter)	114.00 ± 3.00	116.00 ± 3.00	121.00 ± 3.00	NS
Erythrocyte sedimentation rate (mm/h)	52.00 ± 52.00	52.00 ± 5.00	50.00 ± 5.00	NS
Albumin in serum (g/liter)	30.90 ± 0.90	31.00 ± 0.70	31.60 ± 0.80	NS
Serum creatinine (μmol/liter)	88.00 ± 3.00	86.00 ± 4.00	92.00 ± 4.00	NS
Bilirubin in serum (μmol/liter)	15.00 ± 2.00	20.00 ± 5.00	20.0 ± 4.00	NS
S-alkaline phosphatase (μkat/liter)	9.70 ± 2.10	10.40 ± 1.80	9.80 ± 1.50	NS
ASAT (μkat/liter)	0.75 ± 0.12	1.59 ± 0.72	0.93 ± 0.17	NS
ALAT (μkat/liter)	0.69 ± 0.13	0.72 ± 0.13	0.83 ± 0.22	NS

[a] ANOVA, analysis of variance; NS, not significant; TSF, triceps skin fold; AMC, arm muscle circumference; REE, resting energy expenditure; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase.
[b] Mean ± SE.

Table 3 *Physiological and functional variables*

Mean values of all observations during the follow up period ± SE.

	Placebo	Prednisolone	Indomethacin	ANOVA[a] *P* value
Pulse rate (beats/min)	85.00 ± 1.00	82.00 ± 1.00	81.00 ± 1.00	0.03[b]
Systolic blood pressure (mmHg)	130.00 ± 2.00	131.00 ± 2.00	132.00 ± 2.00	NS
Diastolic blood pressure (mmHg)	78.00 ± 1.00	80.00 ± 1.00	79.00 ± 1.00	NS
Body temperature (°C)	37.00 ± 0.06	36.90 ± 0.04	36.80 ± 0.05	NS
Respiratory frequency (breath/min)	21.00 ± 1.00	21.00 ± 0.40	20.00 ± 1.00	NS
Handgrip strength (kg)	18.80 ± 0.80	23.80 ± 1.00	18.80 ± 0.80	0.001[c]
Fatigue (visual analogue scale)	4.40 ± 0.30	4.40 ± 0.20	4.10 ± 0.20	NS
Pain (visual analogue scale)	2.90 ± 0.20	3.0 ± 0.20	1.80 ± 0.20	0.001[d]
Use of analgetic agents, yes/no[e] (ratio)	73/49 (1.49)	72/62 (1.16)	26/90 (0.29)	0.001[f]
Karnofsky index	66.00 ± 3.00	73.00 ± 2.00	75.00 ± 2.00	0.03[g]

[a] ANOVA, analysis of variance.
[b] Placebo *vs* Prednisolone and Placebo *vs* Indomethacin.
[c] Placebo *vs* Prednisolone and Indomethacin *vs* Prednisolone.
[d] Placebo *vs* Indomethacin and Prednisolone *vs* Indomethacin.
[e] The use of one or more than two additional analgetics.
[f] Prednisolone *vs* Indomethacin and placebo *vs* Indomethacin.
[g] Placebo *vs* Indomethacin and Prednisolone *vs* placebo.

regulators and key factors in cell growth control, malignant transformation, and carcinogenesis (4).

The present study supports recent suggestions that eicosanoids may play an important role in determining outcome in progressive clinical cancer. Our results demonstrate for the first time that therapeutically effective, nontoxic doses of indomethacin may retard progression of solid tumor disease. This conclusion was based on the facts that indomethacin maintained Karnowsky index at a significantly higher level and almost doubled survival time compared to placebo treatment. Prednisolone had the same effect to maintain Karnowsky index, but had a less clear effect on survival as also found in animal experimentation.[3] It may be argued that the observed effects were not quantitatively impressive, and from a strict statistical point of view it is obvious that our study has only confirmed a borderline significance ($P < 0.07$) in favor of any single anti-inflammatory treatment, since the original protocol was not designed to compare indomethacin alone to placebo. An individual subgroup comparison is statistically appropriate only when any of the three patient groups did not ($P < 0.05$) belong to the main population. However, we find it clinically relevant to regard indomethacin as a significant drug in palliation of cancer patients with generalized disease where no other alternative exists. This is based on the results in the present study, an attractive theoretical biological concept, and published epidemiological support for a positive effect, including a large body of experimental information obtained by ourselves and others. In this context it is important to emphasize that the majority of established treatment options in clinical use have never been evaluated in placebo-controlled trials.

We observed no serious complications to indomethacin treatment, although the patient population had an age span where gastric ulcer and gastrointestinal bleedings should be expected to occur. Although

Table 4 *Nutritional state during follow-up*

Mean values of all observations during the follow-up ± SE.

	Placebo	Prednisolone	Indomethacin	ANOVA[a] *P* values
Body weight (kg)	64.6 ± 1.5	69.7 ± 1.2	62.5 ± 1.3	0.003[b]
Triceps skinfold (mm)	10.4 ± 0.4	10.2 ± 0.4	10.6 ± 0.4	NS
Upper arm circumference (cm)	26.0 ± 0.4	27.0 ± 0.3	25.4 ± 0.3	0.006
Arm muscle circumference (cm)	22.8 ± 0.3	23.8 ± 0.3	22.0 ± 0.3	0.001[c]
Total body potassium (mmol)	2773.0 ± 101.0	2998.0 ± 95.0	2818.0 ± 109.0	NS

[a] ANOVA, analysis of variance.
[b] Prednisolone.
[c] Prednisolone.

[3] Unpublished results.

Table 5 *Blood chemistry*

Mean values of all observations during the follow-up period ± SE.

	Placebo	Prednisolone	Indomethacin	ANOVA[a] *P* values
Hemoglobin concentration (g/liter)	118.00 ± 2.00	117.00 ± 2.00	114.00 ± 2.00	NS
WBC count (10^9/liter)	10.00 ± 0.40	10.30 ± 0.40	8.20 ± 0.30	0.0003[b]
Thrombocyte count (10^9/liter)	310.00 ± 15.00	344.00 ± 11.00	315.00 ± 12.00	NS
Sedimentation rate (mm)	53.00 ± 3.00	49.00 ± 3.00	51.00 ± 4.00	NS
C-reactive protein (mg/liter)	54.00 ± 4.00	48.00 ± 5.00	49.00 ± 5.00	NS
Protein in serum (g/liter)	69.40 ± 1.00	69.50 ± 0.70	68.00 ± 0.80	NS
Albumin in serum (g/liter)	30.80 ± 0.60	32.40 ± 0.50	32.00 ± 0.60	NS
T4 (nmol/liter)	100.00 ± 3.00	100.00 ± 2.00	106.00 ± 3.00	NS
Free T4 (pmol/liter)	13.20 ± 0.40	12.80 ± 0.40	12.50 ± 0.30	NS
T3 (nmol/liter)	1.39 ± 0.05	1.41 ± 0.04	1.51 ± 0.04	NS
Free T3 (pmol/liter)	3.66 ± 0.14	3.82 ± 0.15	3.98 ± 0.15	NS
rT3 (nmol/liter)	0.48 ± 0.02	0.46 ± 0.02	0.52 ± 0.03	NS
Thyroid-stimulating hormone (mU/liter)	2.25 ± 0.19	1.76 ± 0.08	3.28 ± 0.64	0.01[c]
Sodium (mmol/liter)	135.00 ± 1.00	136.00 ± 1.00	137.00 ± 1.00	NS
Potassium (mmol/liter)	4.10 ± 0.06	4.30 ± 0.05	4.20 ± 0.06	NS
Calcium (mmol/liter)	2.30 ± 0.02	2.30 ± 0.01	2.30 ± 0.01	NS
Serum creatinine (μmol/liter)	93.00 ± 3.00	110.00 ± 7.00	109.00 ± 4.00	NS
Serum bilirubin (μmol/liter)	24.00 ± 4.00	25.00 ± 4.00	13.00 ± 2.00	0.02[d]
S-alkaline phosphatase (μkat/liter)	11.00 ± 1.00	11.00 ± 1.00	9.00 ± 1.00	NS
ASAT (μkat/liter)	0.80 ± 0.10	1.00 ± 0.10	0.70 ± 0.10	NS
ALAT (μkat/liter)	0.60 ± 0.10	0.90 ± 0.10	0.40 ± 0.10	0.004[e]

[a] ANOVA, analysis of variance.
[b] Placebo *vs* Indomethacin, Prednisolone *vs* Indomethacin.
[c] Prednisolone *vs* Indomethacin.
[d] Placebo *vs* Indomethacin, Prednisolone *vs* Indomethacin.
[e] Placebo *vs* Indomethacin, Prednisolone *vs* Indomethacin.

it is possible that glucocorticoid steroids may have similar effects as traditional cyclo-oxygenase inhibitors on inflammation and eicosanoid-related biological cascades, we regard indomethacin as the drug of choice in the clinical setting due to theoretically and experimentally less catabolic and immune-attenuating effects on the host compared to potent glucocorticoids. The main effect by indomethacin to prolong survival and to protect the function of patients is not at all clear. The mechanism may include direct effects on tumor-cell proliferation, attenuation of neovascularization in both primary and secondary tumors, as well as the preservation of host resources against the tumor. In addition, a large body of experimental evidence has suggested that indomethacin treatment of tumor-bearing animals and patients may strengthen the immune status, which may be related to the overall treatment effects (4). In experiments on animals, we and others have reported and observed results that may support any or all of these aspects.

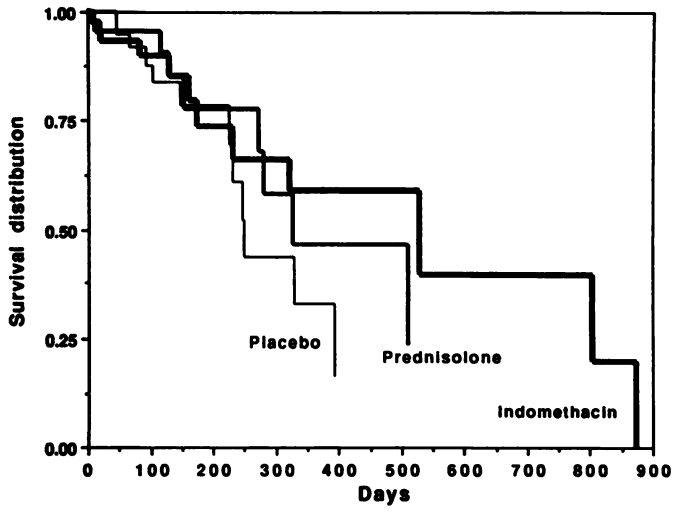

Fig. 1. Survival curves in patient groups treated with either indomethacin, prednislolone or placebo as described in "Materials and Methods." The survival curves differed with a borderline significance ($P < 0.07$).

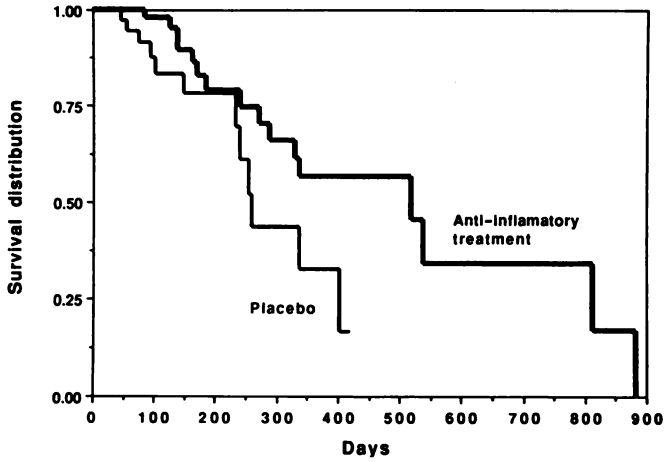

Fig. 2. Survival curves in curve analysis on pooled patients treated with anti-inflammatory drugs (either indomethacin or prednisolone) compared to patients treated with placebo. The survival was significantly prolonged in patients on anti-inflammatory treatment ($P < 0.03$).

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