Randomized Clinical Trial of Adenosine 5′-Triphosphate in Patients With Advanced Non-Small-Cell Lung Cancer

Hendrik J. Agteresch, Pieter C. Dagnelie, Ate van der Gaast, Theo Stijnen, J. H. Paul Wilson

Background: **Extracellular adenosine 5′-triphosphate (ATP) is involved in the regulation of a variety of biologic processes, including neurotransmission, muscle contraction, and liver glucose metabolism, via purinergic receptors. In nonrandomized studies involving patients with different tumor types including non-small-cell lung cancer (NSCLC), ATP infusion appeared to inhibit loss of weight and deterioration of quality of life (QOL) and performance status. We conducted a randomized clinical trial to evaluate the effects of ATP in patients with advanced NSCLC (stage IIIB or IV).** ***Methods:*** **Fifty-eight patients were randomly assigned to receive either 10 intravenous 30-hour ATP infusions, with the infusions given at 2- to 4-week intervals, or no ATP. Outcome parameters were assessed every 4 weeks until 28 weeks. Between-group differences were tested for statistical significance by use of repeated-measures analysis, and reported *P* values are two-sided.** ***Results:*** **Twenty-eight patients were allocated to receive ATP treatment and 30 received no ATP. Mean weight changes per 4-week period were −1.0 kg (95% confidence interval [CI] = −1.5 to −0.5) in the control group and 0.2 kg (95% CI = −0.2 to +0.6) in the ATP group (*P* = .002). Serum albumin concentration declined by −1.2 g/L (95% CI= −2.0 to −0.4) per 4 weeks in the control group but remained stable (0.0 g/L; 95% CI = −0.3 to +0.3) in the ATP group (*P* = .006). Elbow flexor muscle strength declined by −5.5% (95% CI = −9.6% to −1.4%) per 4 weeks in the control group but remained stable (0.0%; 95% CI= −1.4% to +1.4%) in the ATP group (*P* = .01). A similar pattern was observed for knee extensor muscles (*P* = .02). The effects of ATP on body weight, muscle strength, and albumin concentration were especially marked in cachectic patients (*P* = .0002, *P* = .0001, and *P* = .0001, respectively, for ATP versus no ATP). QOL score changes per 4-week period in the ATP group showed overall less deterioration than in the control group—physical scores (−0.2% versus −2.4%; *P* = .0002); functional scores (+0.4% versus −5.5%; *P* = .02); psychologic scores (−0.7% versus −2.4%; *P* = .11); overall QOL score (+0.1% versus −3.5%; *P* = .0001).** ***Conclusions:*** **This randomized trial demonstrates that ATP has beneficial effects on weight, muscle strength, and QOL in patients with advanced NSCLC. [J Natl Cancer Inst 2000;92:321–8]**

Cachexia contributes significantly to the high morbidity and mortality in patients with advanced non-small-cell lung cancer (NSCLC) *(1,2).* Maintenance of weight and of quality of life (QOL) is, therefore, an important issue in the palliative treatment of patients with advanced NSCLC. Dietary counseling *(3,4)* and the use of enteral supplements *(4)* have failed to reverse weight loss. Drugs, including corticosteroids *(5),* cyproheptadine *(6),* hydrazine sulfate *(7),* pentoxifylline *(8),* and anabolic steroids *(9),* were also shown to be ineffective. Prostagens reduced weight loss or increased weight, mainly as fat gain *(10,11).* Although QOL was not influenced by prostagens in all studies *(11–13),* in some studies *(14,15)* it was also improved.

Adenosine 5′-triphosphate (ATP) is a naturally occurring nucleoside triphosphate that plays a central role as an energy source in every cell of the human body. In addition, extracellular ATP is involved in the regulation of a variety of biologic processes, including neurotransmission, muscle contraction, and liver glucose metabolism, by stimulation of purinergic receptors *(16).* Intravenous ATP may offer a novel palliative approach in the treatment of NSCLC. ATP given by daily intraperitoneal injection for 10 days to mice with colon tumors significantly inhibited weight loss *(17).* Recently, in the United States, a small open phase II trial in 15 patients with NSCLC (stage IIIB or IV) *(18)* demonstrated maintenance of weight, QOL, and performance status after treatment with two to four intravenous infusions of ATP (50–65 μg/kg per minute) for 96 hours given at 4-week intervals. These results supported earlier findings from a phase I study in 14 cancer patients *(19).* On the basis of these promising preliminary reports, we conducted a randomized clinical trial to evaluate the effect of ATP infusion on body weight, muscle strength, and QOL in patients with advanced NSCLC (stage IIIB or IV).

Patients and Methods

Patient Eligibility, Randomization, and Study Design

During the period from January 1996 through November 1998, 58 patients were entered in the study. Eligible subjects were patients with histologically or cytologically proven NSCLC of stage IIIB or IV *(20)* and a Karnofsky index of 60% or higher *(21).* Exclusion criteria were as follows: eligibility for curative treatment, liver failure, renal failure (defined as patients needing limitation of fluid intake), respiratory failure (defined as O_2 dependence), heart failure, angina pectoris, cognitive dysfunction, or psychiatric illness. The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center Rotterdam. Written informed consent was obtained from all patients prior to the study.

A randomization list was prepared by the Medical Oncology Trial Office of the Erasmus University Medical Center Rotterdam with the use of block randomization in permutation blocks of four. After baseline measurements, patients were stratified according to tumor stage (IIIB versus IV), previous treatment (chemotherapy versus no chemotherapy), and performance status (Karnofsky index, >70 versus ⩽70); they were then randomly assigned to receive either supportive care and ATP (ATP group) or supportive care alone (control group). Supportive care, provided by the patients' attending physicians,

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included analgesics, antibiotics, anticough medication, antiemetics, bisphosphonates, corticosteroids, and palliative radiotherapy for local control of the primary tumor or metastases.

Patients in the ATP-treatment arm were admitted to the Clinical Research Unit of the University Hospital of the Erasmus University Medical Center Rotterdam to receive a maximum of 10 ATP courses. To keep hospitalization at a minimum for ethical reasons, we chose not to use the schedule used by Haskell et al. *(18,19)* with ATP infusions for 96 hours once every 4 weeks; instead, we gave 30-hour infusions at shorter intervals, i.e., the first seven ATP courses at 2-week intervals, followed by three ATP courses at 4-week intervals. ATP infusions (6.1 mg/mL in 0.9% NaCl) were started beginning at a dose of 20 μg/kg per minute and were increased by increments of 10 μg/kg per minute every 30 minutes until a maximum dose of 75 μg/kg per minute was reached or until the maximally tolerated dose, if this was lower, had been reached. Thereafter, ATP was infused at a continuous rate. If any side effects occurred, the dose was reduced to the last lower dose or further reduced until side effects disappeared. Follow-up was continued until week 28, i.e., 4 weeks after the last ATP course that was given at 24 weeks. Patients in the control arm were followed up at the outpatient department of the Erasmus University Medical Center Rotterdam for 28 weeks. In both groups, anthropometry, blood serum albumin levels, muscle strength, and QOL were assessed before treatment randomization and after randomization at 4-, 8-, 12-, 16-, 20-, 24-, and 28-week periods.

Anthropometry and Muscle Strength

Body height was determined to the nearest centimeter. Body weight was measured with an electronic scale (Seca Ltd., Birmingham, U.K.) to the nearest 0.1 kg.

Strengths of two muscle groups (i.e., elbow flexor muscles and knee extensor muscles) were assessed by use of a hand-held Microfet2^{R} dynamometer (Biometrics Europe, Amersfoort, The Netherlands). This technique has been validated in several groups of patients, mostly in those patients who were limited in muscle strength *(22,23)*. The patient while sitting exerted a maximal force with the 90° flexed right elbow, while the examiner pushed with the dynamometer against the patient's thumb pad until the muscle strength was overcome (break test). Similarly, the patient exerted a maximal force with the 90° flexed right knee, while the examiner pushed with the dynamometer against the patient's ankle until the muscle strength was overcome. The strength of both muscle groups was measured three times at an interval of approximately 10 seconds. Muscle strength was expressed in Newtonmeter (Nm) units and was calculated by dividing the measured mean strength (dynamometer reading) by the distance from the dynamometer position point to the humeral epicondylus medialis (elbow) and the femural epicondylus medialis (knee). The same observer (H. J. Agteresch) carried out all measurements.

Quality of Life

QOL was assessed with the use of The Rotterdam Symptom Checklist (RSCL), a 39-item self-report questionnaire *(24)*. The reliability and validity of the RSCL in cancer patients have been confirmed in both cross-sectional *(25)* and longitudinal *(26,27)* studies in patients with a wide range of cancers. This questionnaire, which assesses symptoms during the preceding week, was filled out by the patients. The RSCL measures scores on four domains: 1) a physical score (23 items), 2) a psychologic score (seven items), 3) a functional score (eight items), and 4) an overall score (one item). Each item is rated on a 4-point scale. Results per item were transformed into standardized scores, ranging from 0 to 100 with the use of the following formula: 100 – [100 × (item scale score – minimum item score)/(maximum score – minimum score)]. A lower score represents a greater level of distress *(24)*.

Statistical Analysis

Differences over time between body weight, serum albumin levels, muscle strength, and QOL scores in the two groups were analyzed according to the "intention-to-treat" principle by repeated-measures analysis of covariance with the use of the linear regression model. To account for the within-patient correlation in the measurements of the dependent variable and, simultaneously, for possible non-normality of the dependent variable, the Generalized Estimating Equations *(28)* approach was followed. These analyses were performed with the SAS procedure Proc Mixed (version 6.12-Windows; SAS Inc., Cary, NC), with the use of the independence working correlation structure. Independent variables in the model were the treatment indicator variable, baseline measurement, measurement time, and interaction between time and treatment. This model assumes a linear relation between measurement and time in both treatment groups, which was checked by adding quadratic time terms. Statistical significance of the treatment effect was assessed by testing the null hypothesis that the coefficients of the treatment indicator and its interaction with time are simultaneously equal to zero. Survival was compared between groups by means of the log-rank test with the use of SPSS (version 6.1.3-Windows; SPSS Inc., Chicago, IL). Two-sided *P* values less than .05 were considered statistically significant.

RESULTS

Data on Patients

Twenty-eight patients were allocated to ATP treatment, and 30 were assigned to no ATP treatment. The trial design is summarized in Fig. 1. Age, tumor stage, performance status, previous treatment, and outcome parameters were similar at baseline between the ATP and control arms. Assessable patients in the ATP group weighed more and had lost more weight than patients in the control group. In both groups, the majority were male (Table 1). However, when the statistical analyses for all outcome parameters were adjusted for age, sex, body weight, weight loss, and histologic type, this did not alter the results in both groups.

Twenty-eight patients in the ATP group received a total of 176 ATP courses. Eleven patients received one to three ATP courses, five received four to six courses, and 12 received seven to 10 courses. Fifty-two infusions of ATP were given as low-dose infusions of 25–40 μg/kg per minute, 47 as middle-dose infusions of 45–60 μg/kg per minute, and 77 as high-dose infusions of 65–75 μg/kg per minute. Sixty-seven percent of the ATP courses were without side effects (36% and 73% of first and subsequent courses, respectively). Side effects were monitored according to the Common Toxicity Criteria (National Cancer Institute) graded on a 4-point scale according to seriousness. During ATP infusions, the most frequently reported side effects (expressed as percent of total number of infusions [n = 176] resulting in the side effects) were of type 1 (chest discomfort, 15%; urge to take a deep breath, 10%; flushing, 5%; nausea, 5%; lightheadedness, 3%; headache, 2%; sweating, 2%; mood alteration–anxiety, 2%; and palpitations, 1%). Few side effects were of type 2 (injection side reaction, 3%), and none were of type 3. Although mild, one side effect was of type 4 (dyspnea, 3%). In patients with chest discomfort during ATP infusion, electrocardiography (ECG) was performed. In no case were ECG changes suggestive of myocardial ischemia detected. The side effects always resolved within minutes of lowering the ATP dose.

Body Weight

In control patients, the mean weight loss over the 28-week study period (expressed as change per 4 weeks) was −1.0 kg (95% CI = −1.5 to −0.5) per 4 weeks, whereas ATP-treated patients experienced no weight loss (0.2 kg; 95% CI = −0.2 to +0.6; *P* for between-group difference = .002; Fig. 2, A). For further analysis, the participants were stratified according to the presence of cachexia prior to the study (⩾5% versus <5% weight loss in relation to weight before the illness; 16 patients in the ATP group and 13 patients in the control group versus 9 patients in the ATP group and 12 patients in the control group). In cachectic patients, progressive weight loss of −1.6 kg (95% CI = −2.1 to −1.1) per 4 weeks was observed in the control group, while no additional weight loss occurred in the ATP group (+0.3 kg; 95% CI = −0.5 to

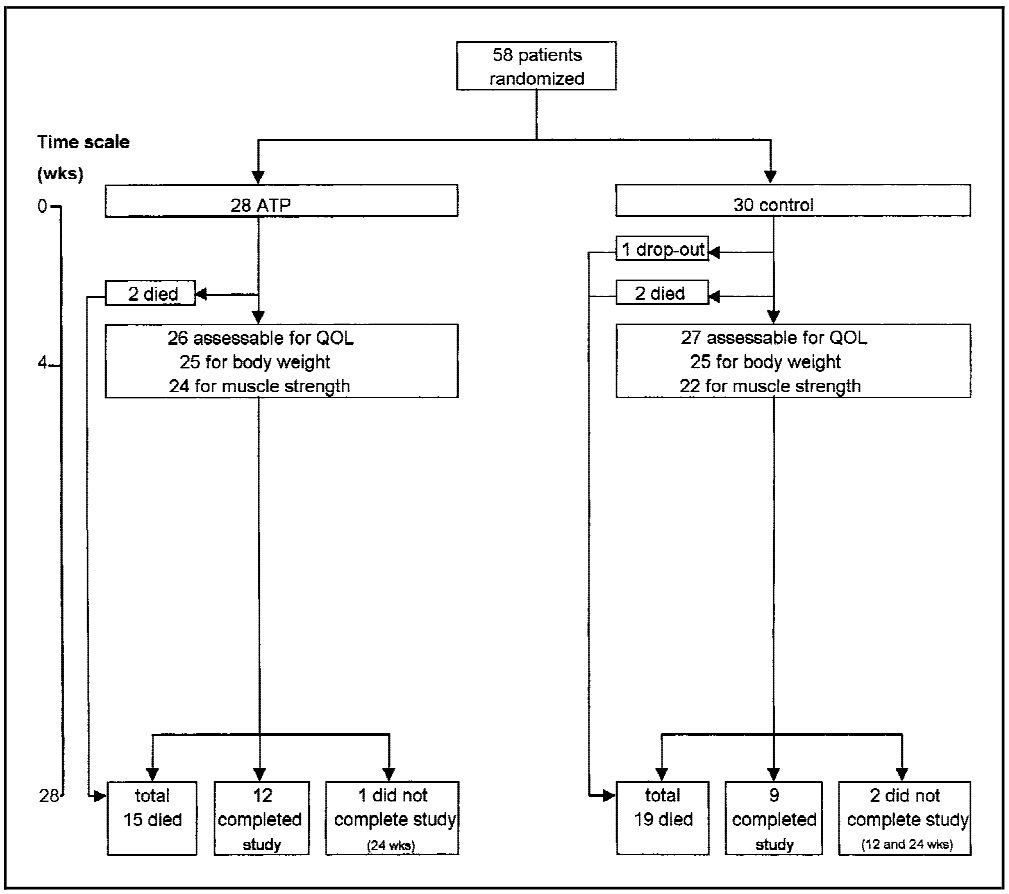

Fig. 1. Flow diagram for the randomized trial of adenosine 5′-triphosphate (ATP) in the treatment of advanced non-small-cell lung cancer. Body weight was not assessable because of hospitalization of one patient in the ATP group and two patients in the control group; muscle strength was not assessable because of hospitalization of two patients in the ATP group and three patients in the control group, and two additional patients in the control group were not assessable because of a technical defect in the dynamometer before randomization. QOL = quality of life.

+1.1; P for between-group difference = .0002). In noncachectic patients, statistical significance between the study groups was not reached (P = .22).

Serum Albumin Levels

Serum albumin concentration (g/L) declined by −1.2 (95% CI = −2.0 to −0.4) per 4 weeks in the control group, whereas no change was detected in the ATP group (0.0 g/L; 95% CI = −0.3 to +0.3; P for between-group difference = .006; Fig. 3). The effect of ATP on albumin was highly significant in patients who were already cachectic at the beginning of the study (P = .0001) but not in noncachectic patients (P = .37).

Muscle Strength

The strength of elbow flexor muscles declined by −5.5% (95% CI= −9.6% to −1.4%) per 4 weeks in the control group, whereas values remained stable in the ATP group (0.0%; 95% CI = −1.4% to +1.4%; P for between-group difference = .01; Fig. 2, B, top). A similar pattern was observed for knee extensor muscles: Muscle strength in control patients decreased by −4.5% (95% CI = −9.7% to −0.7%) per 4 weeks, whereas muscle strength in ATP-treated patients showed no significant change with time (+1.4%; 95% CI = −0.2% to +3.1%; P = .02; Fig. 2, B, bottom). The effect of ATP on the strength of elbow flexor and knee extensor muscles was highly significant in patients who were already cachectic at the beginning of the study (both P = .0001) but not in noncachectic patients (P = .38 and P = .44, respectively).

Quality of Life

During follow-up, patients in the control group showed an impairment in their physical QOL score of −2.4% (95% CI = −4.1% to −0.6%) per 4 weeks, whereas patients in the ATP group showed no change (−0.2%; 95% CI = −1.1% to +0.7%; P for between-group difference = .0002; Fig. 4, A). The functional score deteriorated by −5.5% (95% CI = −9.6% to −1.4%) per 4 weeks in patients in the control group, whereas patients in the ATP group showed no significant change (+0.4%; 95% CI = −1.8% to +2.6%; P = .02; Fig. 4, B). The psychologic score deteriorated by −2.4% (95% CI = −5.9% to +1.1%) per 4 weeks in patients in the control group but showed no significant change in patients in the ATP group (−0.7%; 95% CI = −2.0% to +0.6%; P = .11). With regard to the overall score of QOL, patients in the control group showed a deterioration in QOL by −3.5% (95% CI = −6.5% to −0.5%) per 4 weeks, whereas patients in the ATP group showed no change (+0.1%; 95% CI = −1.8% to +2.0%; P = .0001; Fig. 4, C). The positive effects of ATP on QOL were similar in both cachectic and noncachectic patients.

Comparison of single items contributing to significant differences in physical scores between the ATP and control groups showed beneficial effects of ATP on tiredness (P = .0001), lack of energy (P = .001), appetite (P = .0004), shortness of breath (P = .001), sore muscles (P = .0007), shivering (P = .006), constipation (P = .003), and difficulties in concentrating (P = .0005). Items contributing to the significant difference in functional deterioration between the ATP and the control groups included self-care (P = .009), doing light housework (P = .031), doing heavy housework (P = .002), climbing stairs (P = .016), and walking outdoors (P = .011). Of the

Table 1. Baseline patient characteristics of the randomly assigned and assessable patients in the adenosine 5′-triphosphate (ATP) trial

	ATP*		Control*	
	Randomly assigned (n = 28)	Assessable† (n = 26)‡	Randomly assigned (n = 30)	Assessable† (n = 27)‡
Sex				
Male	20 (71%)	19 (73%)	18 (60%)	16 (59%)
Female	8 (29%)	7 (27%)	12 (40%)	11 (41%)
Age, y	64 ± 13	64 ± 13	61 ± 10	62 ± 11
Tumor histology				
Adenocarcinoma	11 (39%)	11 (42%)	6 (20%)	6 (22%)
Squamous cell carcinoma	10 (36%)	10 (38%)	11 (37%)	10 (37%)
Undifferentiated large-cell carcinoma	4 (14%)	4 (15%)	9 (30%)	7 (26%)
Unspecified	3 (11%)	1 (4%)	4 (13%)	4 (15%)
Chemotherapy as pretreatment				
Yes	12 (43%)	11 (42%)	14 (47%)	13 (48%)
No	16 (57%)	15 (58%)	16 (53%)	14 (52%)
Stage§				
IIIB	13 (46%)	11 (42%)	14 (47%)	13 (48%)
IV	15 (54%)	15 (58%)	16 (53%)	14 (52%)
Karnofsky score				
≤70	12 (43%)	11 (42%)	14 (47%)	13 (48%)
>70	16 (57%)	15 (58%)	16 (53%)	14 (52%)
Prior weight loss, kg‖	5.8 ± 6.5	6.2 ± 6.8	4.9 ± 6.7	4.1 ± 6.8
Prior weight loss, %‖	6.7 ± 7.1	7.1 ± 7.3	6.8 ± 9.7	5.6 ± 9.6
Weight, kg	75.0 ± 16.4	75.1 ± 17.1	68.2 ± 12.3	69.2 ± 12.1
Body mass index, kg/m^2	25.3 ± 5.5	25.5 ± 5.9	23.8 ± 4.0	24.3 ± 4.0
Albumin, g/L	40.7 ± 4.5	40.6 ± 4.6	40.0 ± 4.5	40.5 ± 4.2
Elbow flexor strength, Nm	533 ± 110	541 ± 114	512 ± 116	527 ± 121
Knee extensor strength, Nm	828 ± 177	839 ± 151	797 ± 219	838 ± 207
Physical QOL score¶	78.5 ± 13.7	77.9 ± 13.9	77.2 ± 12.2	78.1 ± 12.3
Psychologic QOL score¶	69.0 ± 23.0	68.8 ± 23.8	70.3 ± 20.2	71.4 ± 19.5
Functional QOL score¶	80.1 ± 19.4	79.9 ± 19.6	77.7 ± 21.6	79.3 ± 22.2
Overall QOL score¶	62.3 ± 21.5	60.7 ± 24.5	57.2 ± 18.4	59.3 ± 18.1

*Scores were expressed as mean ± standard deviation or number (%).

†At least one follow-up analysis was performed.

‡Characteristics for weight and muscle strength, n = 25 and 24, respectively, in the ATP group, and n = 25 and 22, respectively, in the control group.

§*See (20).*

‖Weight loss in relation to weight before illness.

¶Quality-of-life (QOL) scores ranging from 0 to 100; a lower score represents a greater degree of symptoms.

items contributing to the psychologic scores, only the score for irritability (P = .047) was significantly different between the two groups.

Concomitant Supportive Treatment

During the 28-week follow-up period, none of the patients underwent surgery. One patient in the control group was treated with chemotherapy, which consisted of five courses of a combination of cisplatin and etoposide given at 3-week intervals, followed by radiotherapy involving all lesions. Palliative radiotherapy was given to seven patients in the control group and to six patients in the ATP group. Thirteen patients in the control group and nine patients in the ATP group used corticosteroids to treat symptoms of brain edema (four patients in the ATP group and one patient in the control group), dyspnea (four patients in the ATP group and 12 patients in the control group), and nausea (one patient in the ATP group and no patients in the control group).

Survival

Twenty-eight weeks after randomization, the median survival time was 5.6 months (95% CI = 1.1–10.1 months) for patients in the ATP group and 4.7 months (95% CI = 2.5–6.8 months) for patients in the control group (P for between-group difference = .51).

Discussion

Traditional outcome variables in clinical oncology have been survival and tumor response. Although evaluation of the functional status, the QOL, and the body weight of cancer patients is increasingly perceived as a major aspect of cancer treatment *(27,29)*, the number of studies investigating these parameters remains limited.

The aim of our study was to investigate the effect of ATP on body weight and QOL in patients with advanced-stage NSCLC as well as its effect on arm and leg muscle strength as functional and patient-relevant parameters. Since the trial was performed in patients with advanced lung cancer, hand-held dynamometry was chosen because this technique is noninvasive. Clearly, the ideal method for assessing treatment effects regarding QOL would have been a double-blind, placebo-controlled study. However, blinding was not feasible because of the complexity of ATP administration. Some side effects are relatively specific to ATP so that both patients and investigators would have easily recognized that ATP was being given. In addition, there were ethical reasons for not giving 10 placebo infusions to patients with advanced lung cancer with a short life expectancy (3–6 months). Despite these limitations, the remarkably consistent positive effects of ATP on QOL and on objective parameters, such as body weight and serum albumin levels, seem to underline the validity of our results.

During treatment and follow-up, a significant difference in mean weight loss was observed between patients in the ATP group and those in the control group. Patients in the control group lost approximately 1 kg per 4 weeks or 6.5 kg over a 6-month period, whereas patients in the ATP group had an average stable weight over the 6-month period. In cancer patients, loss of body weight is mainly due to loss of fat and of skeletal muscle mass *(30)*. In our study, control patients lost approximately one third of their muscle strength in both arms and legs over a 6-month period, whereas ATP-treated patients lost no muscle strength. The signifi-

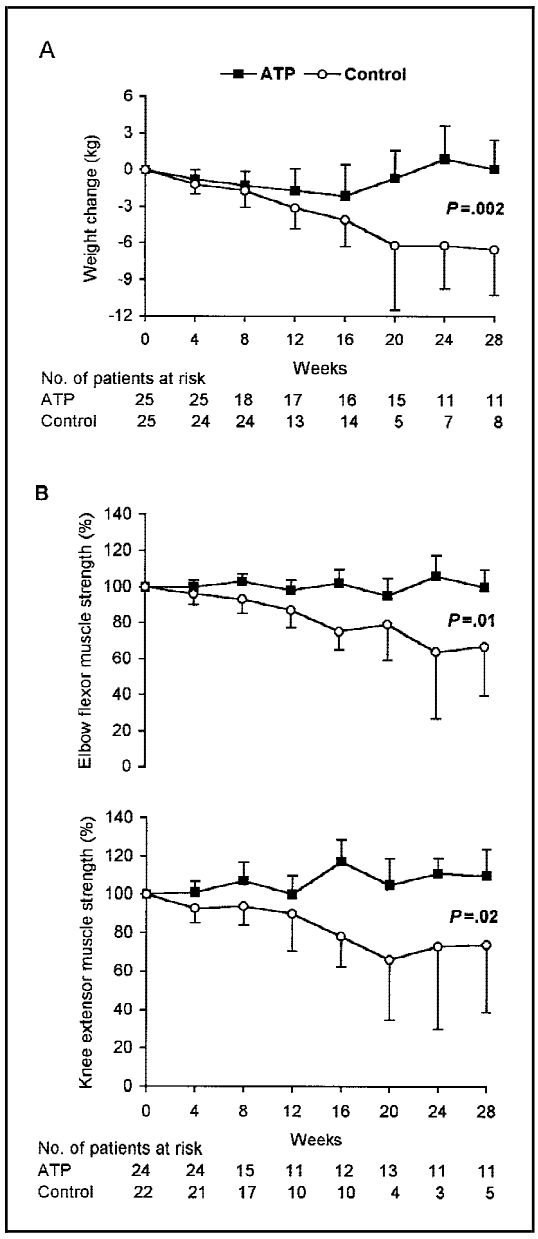

Fig. 2. Changes in **A**) body weight and **B**) elbow flexor (**top**) and knee extensor (**bottom**) muscle strength. **Graphs** represent mean values, and **bars** represent 95% confidence intervals. Two-sided *P* values for differences between patients in the adenosine 5′-triphosphate (ATP) group and patients in the control group were determined with the use of repeated-measures analysis.

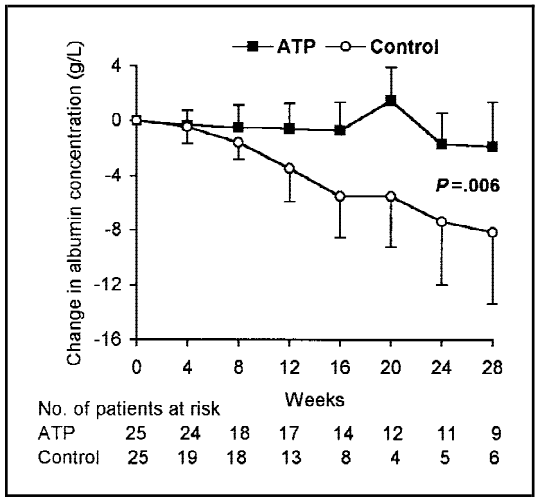

Fig. 3. Changes in serum albumin concentration (mean ± 95% confidence interval). Two-sided *P* value for difference between patients in the adenosine 5′-triphosphate (ATP) group and patients in the control group was determined with the use of repeated-measures analysis.

cant difference between patients in the ATP group and those in the control group in concentration of the nutritional parameter albumin provides a biochemical confirmation of the beneficial effects of ATP on the nutritional and functional status of patients with advanced lung cancer. It is noteworthy that the effect of ATP on weight loss, muscle strength, and serum albumin concentration was especially marked in patients who were already cachectic at the start of the study, whereas no statistical significance was reached in noncachectic patients.

Furthermore, a statistically significant difference in overall scores on the QOL instrument evolved between patients in the ATP group and those in the control group. In the control group, the deterioration expected in patients with progressive cancer was seen, whereas this deterioration was not observed in the ATP group. The QOL of the patients in the control group deteriorated significantly both at the physical (2% per 4 weeks) and functional (5% per 4 weeks) levels, whereas these domains remained practically unchanged in patients in the ATP group. The physical and functional scores were significantly different between patients in the ATP group and those in the control group, whereas the psychologic scores were not different. Furthermore, patients in the ATP group showed a significantly better general activity level, including doing housework, climbing stairs, and walking outdoors, which supports the validity of the beneficial effects of ATP on muscle strength. Items contributing to the better physical scores in patients in the ATP group included lung cancer-related (e.g., shortness of breath) as well as general symptoms. It is noteworthy that the items include two of the most common cancer-related symptoms: tiredness and lack of energy *(31).* Scores for chest pain and coughing did not significantly differ between the two groups ($P = .05$ and $P = .21$, respectively).

In both groups of patients, palliative radiotherapy was given to approximately the same number of patients, whereas more patients in the control group than in the ATP group used corticosteroids. None of the patients used corticosteroids as appetite-stimulating drugs or other appetite stimulators, such as cyproheptadine and megestrol acetate. One ATP-treated patient used marihuana tea for nausea; however, in a recent placebo-controlled study in patients with acquired immunodefi-

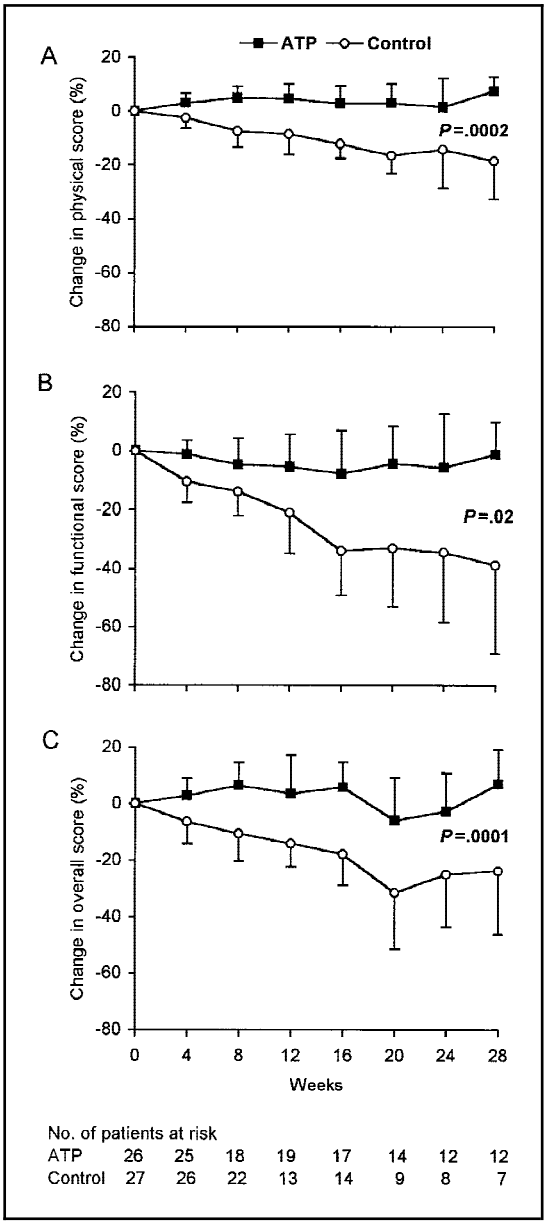

Fig. 4. Changes in The Rotterdam Symptom Checklist quality-of-life (QOL) scores (mean ± 95% confidence interval). **A**) Physical score, **B**) functional score, and **C**) overall score. Two-sided *P* values for differences between patients in the adenosine 5′-triphosphate (ATP) group and patients in the control group were determined with the use of repeated-measures analysis.

ciency disease syndrome *(32)*, no significant effect of dronabinol (the active ingredient of marihuana) on body weight was shown. This finding indicates that differences between the patients in the ATP group and those in the control groups were not due to confounding effects of concomitant supportive treatment.

ATP was administered as a constant intravenous infusion without side effects in the majority of courses; if side effects occurred, they disappeared rapidly when the infusion rate was lowered. The reported side effects were mostly of type 1 and sometimes of type 2. Although during the courses some patients showed dyspnea (type 4), this side effect was mild in nature. Since, in addition, no side effects were observed between the ATP infusions, ATP treatment appears to be a nontoxic therapy in patients with advanced lung cancer.

The mechanisms contributing to the effects of ATP on body weight, muscle strength, and QOL are not well understood. It is unlikely that the beneficial effects of ATP on body weight and QOL would be caused simply by appetite-stimulating effects, since appetite stimulators, such as cyproheptadine *(6)* and corticosteroids *(33)*, did not influence the body weights of cancer patients. Rather, our results would suggest that ATP may also influence specific metabolic pathways. In addition to the well-established role of ATP in cellular metabolism, extracellular ATP appears to be involved in the regulation of a variety of biologic processes, including neurotransmission, muscle contraction, cardiac function, vasodilatation, and liver glycogen metabolism *(16)*. ATP can be released from the cytoplasm of several cell types and interacts with purinergic P1 and, particularly, P2 receptors on the surface of many cells *(16)*. Significantly lower ATP levels have been found in the liver and in the skeletal muscle of tumor-bearing rats *(34)*. Rapaport and Fontaine *(17)* showed that intraperitoneal ATP administration doubled hepatic ATP pools and inhibited weight loss in tumor-bearing mice. These authors suggested that ATP may inhibit Cori cycle activity (i.e., conversion of glucose to lactate in peripheral tissues followed by gluconeogenesis from lactate followed in the liver). Studies in isolated hepatocytes showed that extracellular ATP induced Ca^{2+}mobilization and influx by stimulation of surface P2 receptors *(35)* that are involved in the control of gluconeogenesis *(36)* and glycogenolysis *(37)*. Furthermore, since albumin levels are affected by both nutrition and acute-phase response, it is possible that the stabilization of serum albumin levels by ATP may be caused by inhibition of the acute-phase response. In animals, ATP has been shown to decrease the production of the proinflammatory cytokines interleukin 1 and interleukin 6 *(38)*. This observation is noteworthy, since increased serum levels of these interleukins *(39,40)* have been found in patients with advanced cancer and were suggested to play a prominent role in progressive weight loss in cancer *(41)*. In addition to the effects described above, ATP may have other benefits in oncology. Preclinical studies showed that ATP administration may potentiate the antitumor effects of cytostatics *(42)* and radiotherapy *(43)* and may also have protective effects against radiation tissue damage *(44)*.

In conclusion, our results demonstrate that ATP infusion has marked beneficial effects on the QOL of patients with advanced NSCLC. In patients who are losing weight, ATP prevents further weight loss and maintains muscle strength of both the upper and the lower extremities. ATP can be administered as a constant intravenous infusion without side effects in the majority of courses; if side effects occur, they are mild and transient. In contrast to earlier pharmacologic attempts to reverse cancer cachexia, it appears that ATP might be the first agent with beneficial effects on skeletal muscles of cachec-

tic cancer patients. We conclude that ATP has potential in the palliative management of lung cancer. Further clinical trials using an appropriate placebo control are warranted.

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NOTES

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