Randomized clinical trial of adenosine 5′-triphosphate on tumor growth and survival in advanced lung cancer patients

Hendrik J. Agteresch[a], Sjaak A. Burgers[b], Ate van der Gaast[c], J. H. Paul Wilson[a] and Pieter C. Dagnelie[d]

We recently reported that regular infusions of adenosine 5′-triphosphate (ATP) inhibited loss of body weight and quality of life in patients with non-small cell lung cancer (NSCLC). In the present paper we investigated whether ATP affects tumor growth and survival in the same group of patients. Fifty-eight NSCLC patients (stage IIIB or IV) were randomly assigned to receive either 10 i.v. 30-h ATP infusions every 2–4 weeks over a 24-week period ($n = 28$) or no ATP (control patients, $n = 30$). ATP was given for a median of 6.5 infusions. Differences in time to progression and survival between patients in both groups were tested by means of the log-rank test and Cox regression analysis. Forty-nine patients were evaluable for tumor response. None of the evaluable patients showed a complete or partial response. Median time to progression was 3.9 months [95% confidence interval (CI) = 2.3–5.5] in the ATP group compared to 3.0 months (95% CI = 2.4–3.7) in the control group ($p = 0.71$). Median survival was 5.6 months (95% CI = 1.1–10.1) for the ATP group and 4.7 months (95% CI = 2.6–6.8) for the control group ($p = 0.68$). ATP treatment was associated with a significant increase in survival in the subgroup of weight-losing patients with stage IIIB NSCLC: in this subgroup, median survival was 9.3 months (95% CI = 2.1–16.5) for ATP-treated patients versus 3.5 months (95% CI = 2.3–4.7) for control patients (between-group difference: $p = 0.009$). No significant effect of ATP was observed for weight-losing patients with stage IV NSCLC or for weight-stable NSCLC patients. Although ATP as a single therapy does not lead to tumor regression or increased survival in patients with advanced lung cancer, it may prolong survival in weight-losing patients with stage IIIB lung cancer. The latter finding is intriguing, but requires confirmation in larger clinical trials. *Anti-Cancer Drugs* 14:639–644 © 2003 Lippincott Williams & Wilkins.

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Departments of [a]Internal Medicine, [b]Pulmonary Medicine and [c]Medical Oncology, Erasmus Medical Center, Rotterdam, The Netherlands and [d]Department of Epidemiology, Maastricht University, Maastricht, The Netherlands.

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Correspondence to P. C. Dagnelie, Department of Epidemiology, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands.
Tel: +31 43 3882374; fax: +31 43 3884128;
e-mail: Dagnelie@epid.unimaas.nl

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Introduction

The prognosis of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) remains poor because most tumors are refractory to chemotherapy. The high morbidity and poor overall survival is not only due to progressive tumor growth, but is also aggravated by the high frequency of weight loss in this patient population [1,2]. Adenosine 5′-triphosphate (ATP) may offer a novel approach in the treatment of lung cancer patients.

Administration of ATP has been shown to inhibit growth of various human tumor cell lines [3–8].

Several mechanisms have been proposed: (i) extracellular ATP has been reported to cause arrest of tumor cells in the S phase of cell replication [3,6], (ii) extracellular ATP is thought to induce an adenosine-dependent pyrimidine starvation effect [9–11], (iii) extracellular ATP was reported to induce a decrease in glutathione content of the tumor [9,10] and (iv) increased membrane permeability in response to ATP has been demonstrated in various transformed cells. It has been suggested that this may be due to activation of $P2X_7$ receptors [12–13]. Activation of $P2X_7$ receptors results in formation of non-selective pores which would lead to cell death by either necrosis or apoptosis [14,15].

In experimental tumor models *in vivo* ATP also induced inhibition of tumor growth [8,10,16–20]. In addition, i.p. ATP administration inhibited weight loss and significantly prolonged survival in these animals [9,10,20]. In an uncontrolled phase II study, 15 untreated patients with advanced NSCLC (stage IIIB or IV) were treated with one to seven i.v. ATP courses (50–65 μg/kg/min) for 96 h, administered at 4-week intervals. Although no complete or partial tumor response was seen after the ATP courses, 10 patients showed stable disease. In addition, mean

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body weight and quality of life were maintained at a stable level in the total group [21]. Recently, in a randomized clinical trial, we confirmed that ATP infusions contribute to maintenance of body weight, muscle strength, serum albumin levels, quality of life [22], fat-free mass, arm muscle area, body cell mass and food intake [23] in patients with advanced NSCLC during a 6-month period. In the present paper we report on the effect of ATP on tumor growth and survival in the same group of patients.

Patients and methods

Patient selection

Patients were eligible if they had stage IIIB or IV [24] histologically or cytologically proven NSCLC and a Karnofsky index of 60% or higher [25]. Exclusion criteria were: eligibility for curative treatment; liver failure, renal failure defined as the need for limited fluid intake, respiratory failure defined as O_2 dependence, heart failure, angina pectoris, cognitive dysfunction and psychiatric illness.

The study was approved by the Medical Ethical Committee of the Erasmus Medical Center Rotterdam. Written informed consent was obtained from all patients prior to the study.

Randomization and treatment schedule

A randomization list was prepared by the Medical Oncology Trial Office of the Erasmus Medical Center, Rotterdam using block randomization in permutation blocks of four. After baseline measurements, patients were stratified for tumor stage (IIIB versus IV), prior treatment (chemotherapy versus no chemotherapy) and performance status (Karnofsky score > 70 versus $\leq 70\%$), and 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, included analgesics, antibiotics, anticough medication, antiemetics, bisphosphonates, corticosteroids and intercurrent 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 Erasmus Medical Center, Rotterdam to receive a maximum of 10 ATP courses of 30 h each: seven courses at 2-week intervals, followed by three ATP courses at 4-week intervals. ATP infusions (6.1 mg ATP-Na_2·$3H_2O$ in 1 ml 0.9% NaCl) were started beginning at a dose of 20 μg/kg/min and were increased by increments of 10 μg/kg/min every 30 min until a maximum dose of 75 μg/kg/min, or the maximally tolerated dose if lower, had been reached. Thereafter, ATP was infused at a continuous rate. If any side-effects occurred, the dose was reduced to the last given dose or further until side-effects disappeared.

In both study arms the minimum evaluation of tumor response for all patients included history and physical examination, chest X-ray, and biochemistry. Patients were evaluated for response at 4-week intervals.

Tumor response

Tumor response was evaluated on X-rays or computed tomography scans every 8 weeks by standard WHO criteria. Partial response required $> 50\%$ reduction of the product of the perpendicular diameters of all measurable lesions. Stable disease was defined as $< 50\%$ reduction and $< 25\%$ increase in measurable or evaluable lesions, whereas progressive disease was defined as $> 25\%$ increase in the size of tumor lesions or the appearance a new lesion.

Statistics

Differences in time to progression and survival between patients in the ATP group and patients in the control group were tested by means of the log-rank test. Survival curves were fitted according to Kaplan–Meier. Survival analysis was based on the entire study population according to the intention-to-treat principle. The Cox proportional hazards model was used for survival analysis. Since ATP-treated patients at baseline had higher body weight and lower age (Tables 1 and 2), analyses were repeated including these parameters as covariates. Because of the demonstrated inhibitory effects of ATP on weight loss [22] and the well-known impact of weight loss and tumor stage on survival, a potentially differential

Table 1 Baseline patient characteristics of the 58 randomized patients

	ATP ($n = 28$)	Control ($n = 30$)
Gender		
Male	20 (71%)	18 (60%)
Female	8 (29%)	12 (40%)
Age (years)	64 ± 13	61 ± 10
Tumor histology		
adenocarcinoma	11 (39%)	6 (20%)
squamous cell carcinoma	10 (36%)	11(37%)
undifferentiated large cell carcinoma	4 (14%)	9 (30%)
unspecified	3 (11%)	4 (13%)
Previous chemotherapy		
yes	12 (43%)	14 (47%)
no	16 (57%)	16 (53%)
Stage		
IIIB	13 (46%)	14 (47%)
IV	15 (54%)	16 (53%)
Karnofsky Index		
≤ 70	12 (43%)	14 (47%)
>70	16 (57%)	16 (53%)
Prior weight loss (kg)[a]	5.8 ± 6.5	4.9 ± 6.7
Prior weight loss (%)[a]	6.9 ± 7.1	6.8 ± 9.7
Weight (kg)	75.0 ± 16.4	68.2 ± 12.3
Body mass index (kg/m^2)	25.3 ± 5.5	23.8 ± 4.0

Findings are expressed either as a percentage in brackets or as mean ± SD.
[a]Weight loss in relation to pre-illness weight.

Table 2 Baseline characteristics of the subgroup of stage IIIB patients with 5% or greater weight loss at enrolment

	ATP ($n = 8$)	Control ($n = 8$)
Gender		
Male	6 (75%)	5 (63%)
Female	2 (25%)	3 (37%)
Age (years)	66 ± 14	59 ± 7
Tumor histology		
adenocarcinoma	1 (13%)	0 (0%)
squamous cell carcinoma	4 (50%)	5 (63%)
undifferentiated large cell carcinoma	1 (13%)	2 (25%)
unspecified	2 (25%)	1 (12%)
Previous chemotherapy		
yes	3 (37%)	3 (37%)
no	5 (63%)	5 (63%)
Karnofsky Index		
≤ 70	4 (50%)	4 (50%)
>70	4 (50%)	4 (50%)
Prior weight loss (kg)[a]	9.3 ± 5.2	9.8 ± 3.7
Prior weight loss (%)[a]	10.4 ± 4.5	14.2 ± 7.0
Weight (kg)	78.4 ± 27.8	63.9 ± 16.2
Body mass index (kg/m^2)	26.3 ± 9.0	22.4 ± 5.0

Findings are expressed either as a percentage in brackets or as mean ± SD.
[a]Weight loss in relation to pre-illness weight.

effect of ATP on survival in patients with/without weight loss and patients at different tumor stages was anticipated. For this reason, additional Cox regression models were fitted including as covariates interaction terms between (i) treatment (ATP versus control), (ii) weight loss (≥ 5 versus $< 5\%$) and (ii) tumor stage (IIIB versus IV). The cut-off point of 5% for weight loss was based on previous work on weight loss as a predictor of survival [1]. Results were expressed as median months [95% confidence interval (CI)]. Two-tailed p values below 0.05 were considered statistically significant.

Results

Patients

Fifty-eight patients (38 men and 20 women) were randomized to the ATP ($n = 28$) or control group ($n = 30$). The trial profile is summarized in Figure 1. General baseline characteristics including age, stage, performance status and treatment before inclusion in this trial were similar in the ATP and control group. Patients in the ATP group weighed more than patients in the control group. Patient characteristics are shown in Table 1. Of the 58 patients, nine were not evaluable for tumor response because of concomitant chemotherapy (one patient in the control group), radiotherapy (two patients in the control group), patient refusal (one patient in the control group), hospitalization elsewhere (one patient in the ATP group) and early death (two patients in the ATP group and two patients in the control group). For the subgroup of weight-losing patients with stage IIIB NSCLC, patients characteristics are shown in Table 2. Two extremely heavy patients (114 and 133 kg) in the ATP-treated patient subgroup contributed to the difference in baseline body weight between the two treatment groups.

Treatment

Twenty-eight patients in the ATP group received a total of 176 ATP courses. ATP was given for a median of 6.5 (range 1–10) infusions. Eleven patients received one to three ATP courses, five received four to six courses and 12 patients received seven to 10 courses. Fifty-two infusions of ATP were given as low-dose infusions of 25–40 μg/kg/min, 47 as middle-dose infusions of 45–60 μg/kg/min and 77 as high-dose infusions of 65–75 μg/kg/min. The reasons not completing all ATP cycles were death ($n = 15$), progressive disease ($n = 2$) or patient's refusal ($n = 1$).

As previously reported [26], 64% of ATP courses were without side-effects. Side-effects occurring in the remaining courses were mainly mild cardiopulmonary reactions such as chest discomfort and the urge to take a deep breath (both grade 1) which were transient, resolving within minutes after lowering the ATP infusion rate. These reactions were most common in patients with a history of cardiovascular dysfunction or chronic obstructive pulmonary disease. None of the patients developed hematological toxicity. Between the ATP courses, no side-effects of the ATP treatment were reported.

Tumor response

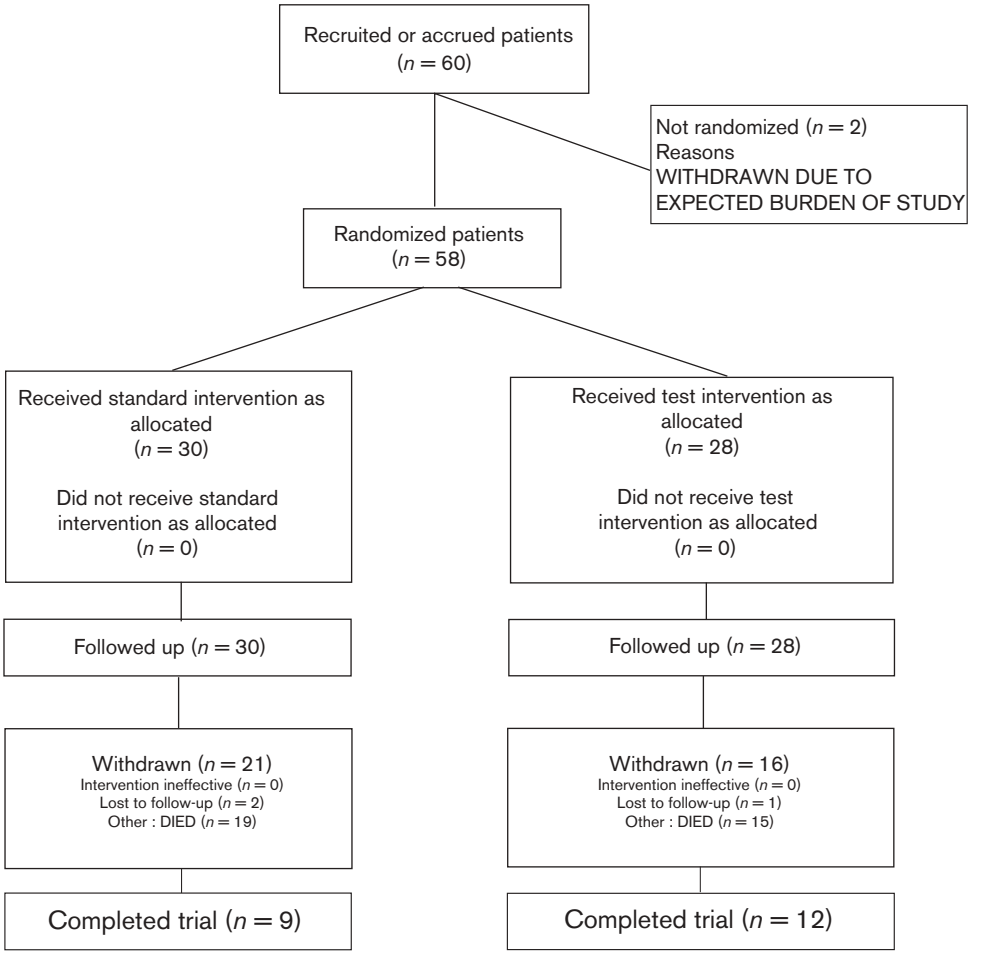
No complete or partial responses were observed. The median time to progression was 3.9 months (95% CI = 2.3–5.5) in the ATP group ($n = 25$) compared to 3.0 months (95% CI = 2.4–3.7) in the control group ($n = 24$; between-group difference: $p = 0.71$).

Survival

Kaplan–Meier plots of survival in all patients given ATP versus no-ATP are shown in Figure 2. Because patients in the ATP group weighed more at randomization, the survival analysis was adjusted for baseline body weight. The median survival time from randomization was 5.6 months (95% CI = 1.1–10.1) for patients in the ATP group and 4.7 months (95% CI = 2.6–6.8) for patients in the control group. There was no statistically significant difference between the two groups ($p = 0.68$). In the ATP group six patients (21%) survived for more than 1 year and in the control group five patients (17%) survived for more than 1 year. On the census date, two of 58 patients (one patient in the ATP group and one patient in the control group) were still alive.

In univariate analysis, weight loss, Karnofsky score, and tumor stage were unfavorable prognostic factors for survival ($p = 0.05$, $p = 0.005$ and $p = 0.05$, respectively). When either of these factors were included as covariates in Cox regression analysis, again no significant effect of ATP on survival was detected (weight loss: $p = 0.15$, Karnofsky score: $p = 0.51$ and tumor stage: $p = 0.49$).

Fig. 1



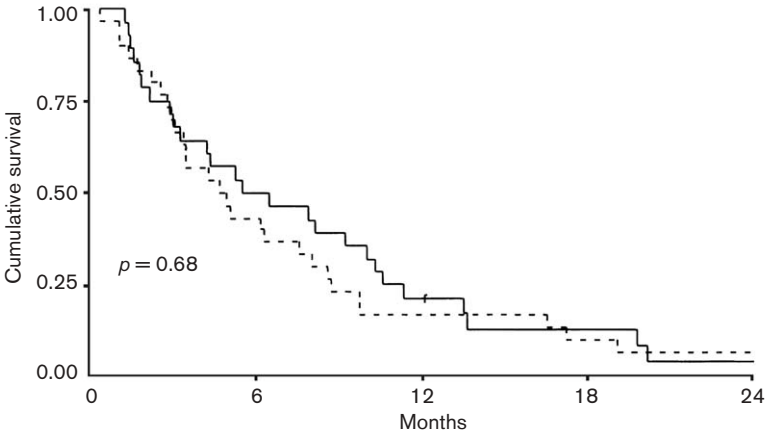
Flow chart of the progress of patients through the trial.

However, multivariate Cox regression analysis including appropriate interaction terms for tumor stage, weight loss and treatment demonstrated a significant survival benefit of ATP-treatment for stage IIIB patients with 5% or greater weight loss at randomization (Fig. 3): in this subgroup, median survival was 9.3 months (95% CI = 2.1–16.5) in ATP-treated patients ($n = 8$) compared to 3.5 months (95% CI = 2.3–4.7) in control patients ($n = 8$; between-group difference: $p = 0.009$). Baseline characteristics of these patients are shown in Table 2. Results remained unchanged (i.e. change in regression coefficient of ATP treatment effect $< 1\%$; $p = 0.015$) when weight at baseline and age were included as potential confounders in the Cox regression model. No significant effect of ATP on survival was seen in weight-losing patients with stage IV (between-group difference: $p = 0.22$): ATP-treated patients ($n = 9$) died after a median of 3.1 months (95% CI = 2.6–3.6) and control patients ($n = 10$) after 2.3 months (95% CI = 0.0–6.8). Furthermore, there was no significant survival difference in weight-stable patients regardless of tumor stage (between-group difference: tumor stage IIIB: $p = 0.26$ and tumor stage IV: $p = 0.83$).

Tumor treatment as co-intervention

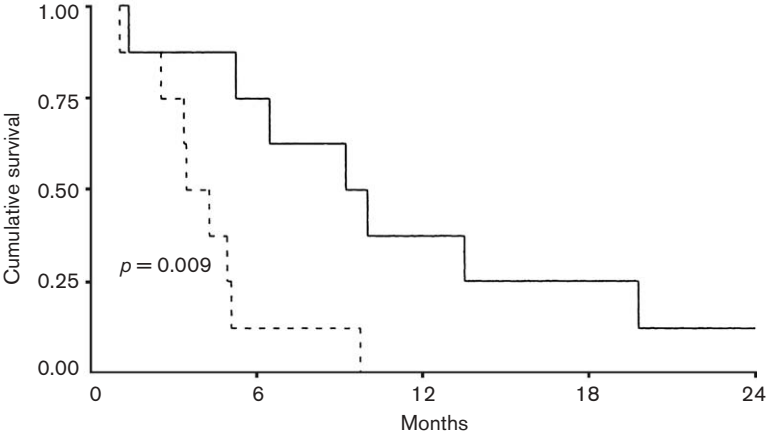
Three months after randomization one patient in the control group (stage IIIB, no weight loss) was treated with combination chemotherapy consisting of five courses of a combination of cisplatin and etoposide, given at 3-week intervals, followed by radiotherapy involving all lesions. One year after randomization, one patient in the ATP group was enrolled in a phase I trial with six courses of PNU-159548 (an alkylcycline). Palliative radiotherapy was administered to seven patients in the control group and to six patients in the ATP group.

Fig. 2



Kaplan–Meier plot of overall survival of ATP-treated ($n = 28$, solid line) and control ($n = 30$, dotted line) patients with advanced NSCLC (stage IIIB or IV).

Fig. 3



Kaplan–Meier survival plot for a subgroup of ATP-treated ($n = 8$, solid line) and control ($n = 8$, dotted line) patients with stage IIIB NSCLC and 5% or greater weight loss at randomization.

Discussion

This is the first randomized clinical trial to examine the effects of i.v. ATP infusions on tumor growth and survival in patients with advanced NSCLC (stage IIIB or IV). In the present study, ATP infusions, given at a frequency of once per 2–4 weeks for 30 h at MTD (maximum 75 μg/kg/min) did not lead to objective tumor response. Furthermore, no effect of ATP on overall survival of this patient group was demonstrated. Despite the relatively small sample size of the present study, the presented Kaplan–Meier plot of survival in the ATP versus control group (Fig. 2) renders it quite unlikely that a significant effect of ATP would have been observed in patients with advanced lung cancer even should several hundreds of patients have been included. In other words, the possibility of a type II error due to lack of power seems implausible based on our data.

Univariate analysis of our data showed that patients with 5% or greater weight loss prior to randomization survived significantly shorter than patients without weight loss, confirming many earlier reports which showed that weight loss is an unfavorable prognostic variable for survival [1,2,27].

Remarkably, multivariate analysis including tumor stage and weight loss as covariates showed that ATP treatment did have a statistically significant ($p = 0.009$) survival

benefit in the subgroup of weight-losing patients with stage IIIB NSCLC. In order to minimize the possibility of a multiple test artifact, we applied a Bonferroni correction which showed that even after this correction the survival difference remained statistically significant ($p = 0.036$). Furthermore, the effect of ATP on survival in this subgroup could not be attributed to differences in baseline characteristics between subjects since both treatment arms were well balanced, except for age and body weight, and if the survival analysis was adjusted for age and body weight, the effect of ATP on survival remained unchanged. Although this subgroup analysis (showing a median survival of 3.5 months in NSCLC patients stage IIIB with weight loss versus 9.3 months in similar ATP-treated patients) provides merely preliminary data which will clearly need confirmation in future rigorous studies, it is tempting to provide a potential biological mechanism for a survival effect of ATP in weight-losing cancer patients. We previously reported [22,23] that ATP inhibited loss of body weight, appetite, muscle mass and muscle strength in NSCLC patients, whereas patients not receiving ATP infusion continued to deteriorate in these parameters. Also, assessment of quality of life using the validated Rotterdam Symptom Checklist in these patients [22] showed that ATP prevented the progressive deterioration (as seen in the control group) on a number of items including lack of energy, shortness of breath, self-care, performing light/heavy housework, climbing stairs and walking outdoors. It is, therefore, possible that the observed survival benefit in these patients with non-metastatic disease is related to the inhibition of loss in weight, muscle mass and performance by ATP. Our observation of lack of such a favorable effect of ATP on survival in weight-losing NSCLC patients of tumor stage IV would not be unexpected in view of the advanced tumor stage of these patients which may restrict any survival benefit of a supportive treatment modality such as ATP which does not influence tumor growth.

In conclusion, despite beneficial effect of ATP on weight loss and quality of life [22], 30-h infusions of ATP once per 2–4 weeks as a single therapy did not affect tumor response nor increase overall survival in patients suffering from NSCLC, stage IIIB or IV. Nevertheless, our data suggest that ATP infusions may prolong survival in a subgroup of weight-losing stage IIIB lung cancer patients, possibly by reducing weight loss. This intriguing finding will require future confirmation in larger clinical trials.

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