



T. Declan Walsh, MSc, FACP, FRCP and Nilo I. Rivera, MD

Adenosine Triphosphate for Cancer Cachexia

Agteresch HJ, Rietveld T, Kerkhofs LGM, *et al.*:
Beneficial effects of adenosine triphosphate on nutritional status in advanced lung cancer patients: a randomized clinical trial. *J Clin Oncol* 2002, 20:371-378.

Rating: •Of importance.

Introduction: Cancer cachexia is associated with increased morbidity and mortality. It is the cause of almost a third of all cancer deaths. It also adversely affects quality of life by invariably producing debilitating fatigue and psychological distress. The biochemical mechanism of cachexia is just beginning to be understood. Increased lipolysis, protein breakdown, and gluconeogenesis have consistently been observed. Effective treatments are currently lacking. Trials using various dietary supplements or pharmacologic agents have produced discouraging results. Progestogen therapy induces weight stabilization or increase, but this consists primarily of fat mass. In animal models of cachexia, depletion of adenosine triphosphate (ATP) levels in the liver and skeletal muscle has been demonstrated. ATP has also been found to be cytotoxic against certain tumor lines *in vitro*. Previous investigations focused on its possible role as an antineoplastic agent. Although significant change in tumor size was not observed, patients who received ATP were found to have better weight than controls. Thus, the hypothesis that ATP has anticachectic activity was formed.

Aims: To evaluate the effects of ATP on the nutritional status of advanced lung cancer patients.

Methods: Fifty-eight stage IIIB or IV lung cancer patients were randomly assigned to receive either ATP infusion with supportive care or supportive care alone. ATP was started at a dose of 20 $\mu\text{g}/\text{kg}/\text{min}$ and increased by 10- $\mu\text{g}/\text{kg}/\text{min}$ increments every 30 minutes until a dose of 75 $\mu\text{g}/\text{kg}/\text{min}$ or the maximum tolerated dose, if this was lower, was reached. This was then administered at a continuous rate over 30 hours at 2-week intervals for the first seven treatments, and then at 4-week intervals for the last three. Weight, midarm circumference (MAC), triceps skin fold (TCF), fat mass (FM), fat-free mass (FFM), body cell mass (BCM), and resting energy expenditure (REE) were measured before the study and at 4-week intervals. Intake of calories, protein, fat,

and carbohydrates was recorded, along with anorexia (using the Rotterdam Symptom Checklist).

Results: Twenty-eight patients were randomly assigned to the ATP group, and 30 to the control group. Eleven patients received one to three ATP courses, five received four to six courses, and 12 received seven to 10 courses. Thirty-six percent of the ATP patients experienced mild and transient side effects, with the most common being chest discomfort (15%) and urge to take a deep breath (10%). The rest had no significant side effects. Because of increased dropout rates among control patients by the twenty-eighth week, statistical analysis for BCM, food intake, and REE was only performed before randomization and at the eighth and sixteenth week. Weight change over the 28-week study period was significantly worse in the control (-1.0 kg / 4 wk) than in the ATP group (+0.2 kg). MAC declined in the control group (-1.8%/4 wk) but increased (+1.1%) in the study group. A loss was observed in FM, FFM, and BCM in the control patients, but not in those who received ATP. Caloric intake decreased in the control group but increased significantly in the ATP group. This finding is due to a difference in the intake of all three nutrients between the two groups. Appetite did not change in the ATP group, but it decreased in the control group. There was no difference in the change in REE between the two groups.

Conclusions: ATP improves nutritional status in patients with advanced lung cancer by maintaining energy intake without reducing REE.

Editors' Comments:

Data on muscle strength and quality-of-life measurements from this same study were previously published (Agteresch *et al.*, *J Natl Cancer Inst* 2000, 90:321-328). In that report, muscle strength and quality of life declined in control patients but did not change in the ATP group. The finding that nutrient ingestion was decreased in the control group but that REE was similar in both groups suggests that ATP maintains metabolic balance by inhibiting further diminution of energy intake without reversing the already elevated energy expenditure. The benefit of ATP appears to be in preventing further decline in nutritional and functional status produced by the cachectic process. Accordingly,

treatment should ideally be given at the earliest evidence of cachexia when patients still have good functional status.

The study introduces a promising therapeutic option for cancer cachexia. However, there are two major drawbacks. First, side effects were observed in about a third of the patients. Although these were described as mild and transient in the present study, in a phase II trial by Haskell *et al.* (*Invest New Drugs* 1998, 16: 81–85), 80% of the patients had adverse events at a dose of 50 µg/kg/min. These adverse effects consisted of chest pain, dyspnea, coughing, anxiety, insomnia, and hot flushes. Six of 15 patients had severe side effects, with two developing life-

threatening dyspnea. Thus, the safety of ATP administered at these doses remains in question. Second, infusion for 30 hours would require hospital admission and monitoring. This would clearly incur additional cost and inconvenience for patients. Unless strong evidence proving unequivocal benefit can be demonstrated, such treatment would be difficult to justify. Further studies should focus on determining optimal doses, timing of treatment, long-term benefit, more in-depth quality-of-life measures, patient satisfaction, and cost-effectiveness. Until then, ATP should rightfully remain a promising investigational drug.