Original Article

Randomized Clinical Trial on the Effects of Adenosine 5'-Triphosphate Infusions on Quality of Life, Functional Status, and Fatigue in Preterminal Cancer Patients

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Abstract

Context. One potential agent to improve symptoms and quality of life (QoL) in advanced cancer patients is adenosine 5'-triphosphate (ATP). Several reports suggest that ATP may positively affect QoL and survival in patients with advanced non-small-cell lung cancer.

Objectives. To investigate the effects of ATP infusions on QoL parameters in patients with preterminal cancer of mixed tumor types.

Methods. Ninety-nine preterminal cancer patients were randomly allocated to receive either ATP intravenously weekly (8–10 hours/week, with maximum 50 μg/kg.minute) for eight weeks or receive no ATP (control group). QoL parameters were assessed until eight weeks and analyzed by repeated-measures analysis of covariance.

Results. Fifty-one patients were randomized to the ATP group and 48 to the control group. Unexpectedly, in the untreated control group, most of the outcome parameters did not deteriorate but remained stable or even significantly improved over time. Between the ATP and control groups, no statistically significant differences were observed for the large majority of outcome parameters, except for the strength of elbow flexor muscles in favor of the control group.

Conclusion. ATP infusions, at the dose and schedule studied, did not have a significant effect on QoL, functional status, or fatigue in preterminal cancer

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Key Words
ATP, cancer, functional status, quality of life

Introduction

Cancer is one of the most common causes of death in the Western world.[1] Despite modern treatment advances, approximately 50% of all cancer patients still die of their disease. Preterminal cancer patients often suffer from multiple symptoms, such as pain, fatigue, dyspnea, anorexia, and cachexia, all of which have a negative impact on their functional status and quality of life (QoL).[2–6] The pathophysiology of these symptoms in advanced cancer is not fully understood. Some symptoms, such as fatigue and the anorexia-cachexia syndrome, are thought to be caused by a state of chronic inflammation with elevated levels of cytokines, produced by the tumor or by the host immune system in response to the tumor.[7,8] Elevated serum concentrations of interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF)-α have been found in cancer patients, and the concentration of these cytokines seems to be correlated with tumor progression.[9] Treatment options to reverse these symptoms and thereby improve QoL in preterminal cancer patients are limited.[10,11]

One potential agent to improve symptoms and QoL in advanced cancer patients is adenosine 5'-triphosphate (ATP). ATP is a naturally occurring nucleotide that is present in every cell of the human body. Although ATP is primarily known for its role in intracellular energy metabolism, it is also widely distributed outside the cell. Extracellular ATP and its breakdown product, adenosine, are involved in the regulation of numerous biological processes by means of P1 and P2 purinergic receptors.[12] Recently, our group showed that ATP inhibits the release of TNF-α in stimulated whole blood by means of $P2Y_{11}$ receptors and stimulates the release of IL-10 by means of $P2Y_{12}$ receptors.[13,14] Furthermore, based on the finding of reduced levels of ATP in the skeletal muscle of cancer patients,[15] it has been hypothesized that cancer and/or its treatment lead to a defect in the mechanism for regenerating ATP in skeletal muscle, thereby compromising the ability to perform mechanical tasks.[16] Another hypothesis is that extracellular nucleotides, such as ATP, could play an important role in restoring the energy balance by adenosine monophosphate (AMP)-activated protein kinase (AMPK) activation. It was recently shown that extracellular nucleotides (ATP, adenosine diphosphate (ADP), uridine triphosphate (UTP)) and adenosine, the breakdown product of ATP, independently induce the activation of AMPK in human endothelial cells.[17] AMPK stimulates pathways that increase energy production (glucose transport, fatty acid oxidation) and switches off pathways that consume energy (lipogenesis, protein synthesis, gluconeogenesis).[18]

Results of an earlier randomized clinical trial (RCT)[19] showed that regular intravenous infusion of ATP of 30 hours, given at two- to four-week intervals over a period of 24 weeks, had marked beneficial effects on muscle mass, muscle strength, fatigue, and QoL in patients with advanced (Stage IIIB/IV) non-small-cell lung cancer (NSCLC). ATP treatment also was associated with a highly significant survival benefit in weight-losing patients with Stage IIIB NSCLC.[20]

Based on these previous results, we initiated an RCT to investigate the effects of ATP infusion on QoL, functional status, fatigue, nutritional status, and survival in preterminal cancer patients with mixed tumor types.[21] Results showed a significant advantage of 8- to 10-hour ATP infusions on survival and triceps skinfold thickness during the eight-week intervention period; in weight-stable patients, and in lung cancer patients, the survival benefit of ATP even persisted over six-month follow-up.[22] In this article, we report the effects of ATP infusions on QoL parameters in the same study population of preterminal cancer patients.[22]

Methods

Patients

Eligible for the study were patients with histologically or cytologically confirmed cancer,