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Research Article

# Variations in Blood Adenosine Triphosphate Levels in Oncology Patients Before, During and After Chemotherapy Treatments: An Exploratory Study

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## Abstract

Cancer Related Fatigue (C-RF) may be compounded by chemotherapy whose incidence increases from 61% at diagnosis to 96% after treatment. Exacerbation of C-RF parallels the initiation of chemotherapy and typically abates by six months after conclusion of the therapy. It is a major factor in the quality of life of the cancer patient. We measured whole blood, red blood cell and buffy coat ATP levels before starting chemotherapy, serially during the treatments and six months after their conclusion. Our results showed statistically significant reductions in whole blood and red blood cell ATP levels. There was a statistically significant increase of buffy coat ATP levels from nadir to recovery values. Acceleration of recovery of the ATP deficiencies identified might be accomplished by using yang notifying traditional Chinese herbs such as Herba Cistanche and Cordyceps. Panax ginseng *in vitro* increases ATP levels in cultured liver and muscle cells. Reversal of C-RF and normalization of ATP levels *in vivo* by such agents would establish deficient ATP levels as a contributing cause of C-RF and warrant further study.

**Keywords:** ATP; Cancer related fatigue; Cordyceps; Ganoderma; Ginseng; Herba Cistanche

## Introduction

Approximately 1.2 million new cases of invasive cancer are diagnosed in the United States annually [1]. Many of these patients receive chemotherapy in the neoadjuvant or adjuvant setting, aside from management of metastatic disease. Those patients receiving neo adjuvant or adjuvant chemotherapy receive such treatment for a limited period of time. They afford an opportunity to measure baseline, intra therapeutic and recovery values of select factors. Cancer related fatigue is present in as many as 61% of the patients at diagnosis and is not relieved by rest or sleep [2,3]. The large number of persons affected, therefore, renders this a significant public health issue.

The lassitude of C-RF does not correlate with either hematocrit or hemoglobin levels. Persons with a malignant neoplasm may experience weight loss even though the burden of tumor cells is relatively small. Over decades, many of the chemotherapy patients of MH have been checked for hypoadrenalism or hypothyroidism as a possible etiology of C-RF with nearly universally normal results [4]. The onset of this additional dimension of tiredness typically follows within four to six weeks after the initiation of chemotherapy and begins to improve similarly four to six weeks after completion of the treatments. Patients frequently use the words "tiredness", "fatigue", "brain fog" and "loss of energy" to describe what they experience.

Glucose is the source of energy for the mammalian cell. It is metabolized in the mitochondria to produce a high energy triple bonded phosphate, Adenosine Triphosphate (ATP). ATP is the body's chemical battery in which energy is stored for subsequent use. Cleavage of one of the phosphate atoms, breaking a high energy triple bond, makes that potential chemical energy available for a variety of functions. It drives molecular pumps and enables actin and myosin fibers to contract thus producing muscle movement. ATP powers intracellular pumps that transport some chemotherapeutic agents out of cells and plays a role in the development of multi drug resistance [5]. Multi drug resistance could possibly be part of an organism's genetically encoded mechanism to survive chemically hostile changes in its milieu. It has been suggested that ATP depletion may play a role in apoptosis of malignant cells [6]. In this context, ATP depletion could provide a survival advantage to an organism which has contracted a malignancy. A consequence of these possible pathways could be fatigue due to underlying ATP reduction.

Each mole of glucose metabolized in the tricarboxylic acid cycle (Krebs cycle) produces a net increase of 38 moles of ATP [7]. This is in contrast to the glycolytic pathway (Embden-Meyerhoff) in which each mole of glucose yields only 2 moles of ATP. Glycolysis as the source of energy for most cancer cells and plants was proposed by Warburg in 1956, a finding for which he was awarded the Nobel Prize [8]. Could the presence of a malignancy in the organism thereby produce a metabolic drain because of the inefficient metabolism of the glycolytic pathway typically utilized by the cancer cells? Could cytotoxic chemotherapeutic drugs be another pathway for reduction of ATP production?

Based on the observed parallel timelines of initiation of chemotherapy and onset or worsening of fatigue, it was logical, therefore, to study longitudinally the ATP levels of patients receiving antineoplastic chemotherapy to see if they might diverge from their own baseline. There is no standard as to which assay is to be employed and results vary according to the assay applied [9]. We studied whole blood, red blood cell and buffy coat ATP levels before, during treatment and 6 months after the chemotherapy was completed. In so doing, each patient represents their own control [9].

## Materials and Methods

This study was approved by the Institutional Review Board of NorthShore University Health System ( 2650 North Ridge Avenue;

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| Patient # | Diagnosis | Chemotherapy regimen |
|---|---|---|
| 1 | Ovarian carcinoma (ca) | Carboplatin + paclitaxel |
| 2 | Non-small cell lung ca | Carboplatin + paclitaxel |
| 3 | ca of cecum | 5-fluorouracil + leucovorin |
| 4 | Chronic lymphocytic leukemia | Chlorambucil (oral) |
| 5 | Non-small cell lung ca | Carboplatin + paclitaxel |
| 6 | Non-Hodgkin's lymphoma | Cyclophosphamide +Doxorubicin + Oncovin + Prednisolone (CHOP) |
| 7 | Invasive breast ca | Doxorubicin + cyclophosphamide x 4 --> local radiation therapy --> paclitaxel x 4 |
| 8 | Invasive breast ca | Ibid |
| 9 | Invasive breast ca | Doxorubicin + cyclophosphamide x 4 |
| 10 | Invasive breast ca | Doxorubicin + cyclophosphamide x 4 --> local radiation therapy --> paclitaxel x 4 |
| 11 | Invasive breast ca | Doxorubicin + cyclophosphamide x 4 --> paclitaxel weekly x 12 |
| 12 | Non-Hodgkin's lymphoma | CHOP x 6 --> rituximab maintenance |
| 13 | Ovarian ca | Carboplatin + paclitaxel |
| 14 | Non-Hodgkin's lymphoma (mantle cell) | Fludarabine + cyclophosphamide |
| 15 | Colon ca | CPT-11 + 5FU + leucovorin |
| 16 | Non-Hodgkin's lymphoma | Etoposide + solu-Medrol + cytarabine + cis-Platinum + rituximab |
| 17 | Non-Hodgkin's lymphoma | Rituximab + CHOP |
| 18 | Invasive breast ca | Doxorubicin + cyclophosphamide |
| 19 | Invasive breast ca | Doxorubicin + cyclophosphamide |

**Table 1:** Diagnoses and treatments received either as neo adjuvant or adjuvant therapy by the 19 evaluable patients.

The abbreviations used denote: ca = carcinoma; CPT-11 = irinotecan; CHOP = Cyclophosphamide + doxorubicin + Oncovin + Prednisolone. They were considered evaluable only if their treatments were given for a limited period of time and their baseline, nadir and 6 month post completion of chemotherapy ATP levels were obtained and successfully resulted.

Evanston, IL 60201) when it was Evanston Hospital. Informed consent was obtained from 26 patients prior to initiation of limited term neo adjuvant, adjuvant, or remission inducing chemotherapy from October 4, 1999 through October 19, 2001. Some of the patients did have nodal involvement. The diagnoses of the patients and the chemotherapy regimens employed are shown in table 1. Seven patients for whom complete data sets were not available were excluded from the data analysis. This study was conducted over a decade ago and therefore some of the treatment regimens listed appear dated. Nonetheless, the ATP data are valid and the study's findings pertain to current practices. Despite the time interval between the collection of the data and submission of this report (2017), all the chemotherapeutic agents listed are still in clinical use.

A 7.5 cc yellow top (ACD solution) vial of blood was drawn on day 1 of each treatment cycle (prior to administration of the chemotherapeutic agents), monthly x 3 after completion of the course of chemotherapy and once 6 months after completion of the chemotherapy treatments.

A standard assay for ATP was performed using a commercially available kit produced by sigma diagnostics (P.O. Box 14508; St. Louis, MO 63178). Measurements were conducted using a spectrophotometer at 340 nm by the study's Ph.D. biochemist, SH. The results in micromoles/deciliter were tabulated and statistical significance determined using two methods: the T-test for difference between means sections; and the Wilcoxon signed rank test for difference in medians (NCSS8; 329 North 1000 East; Kaysville, UT 84037).

The ATP assays were conducted on whole blood and then, after centrifugation, on the RBC's. By subtracting the level measured for RBC's from the value for whole blood, the ATP level for the buffy coat was derived. The pretreatment baseline values from day 1 were compared to the lowest value attained during treatment and to the single value obtained 6 months after completion of the chemotherapy treatments.

## Results

Table 1 presents the patients and their diagnoses. Twelve women and 7 men for whom the complete data sets were available were studied. The distribution of patients by diagnosis was as follows: 7 patients with breast carcinoma; 2 patients with colorectal carcinoma; 2 patients with non small cell lung carcinoma; 6 patients with non Hodgkin's lymphoma; 2 women with ovarian carcinoma. None had distant metastases at entry into the study. The one patient with chronic lymphocytic leukemia did not have visceral disease. The ATP levels are reported in micromoles/deciliter. The mean +/- Standard Error of the Mean (SEM) levels of ATP are shown in table 2. The p values for comparisons are shown for the T-test for difference between means followed by the p value for the Wilcoxon signed rank test for differences in medians.

All of the results below are reported as micromoles/deciliter. For whole blood, the ATP levels showed a Statistically Significant (SSIG) decline from baseline to nadir: 41.02 +/- 1.55 to 37.03 +/- 0.84 ($p = 0.002$; $p = 0.002$). The recovery from nadir: 37.03 +/- 0.84 to 42.20 +/- was also SSIG ($p = 0.002$; $p = 0.003$).

The red blood cells ATP levels dropped from baseline levels of 29.77 +/- 1.90 to 26.63 +/- 1.24 at nadir ($p = 0.028$; $p = 0.027$). However, the six month post treatment values did not show recovery at all: 26.63 +/- 1.24 to 26.85 +/- 1.13 ($p = 0.87$; $p = 0.359$).

The mathematically derived baseline buffy coat values (whole blood ATP level minus RBC ATP level) were lower than either the whole blood or red blood cells baseline levels. There was no significant

| Case | Whole Blood | | | RBC | | | Buffy Coat | | |
|---|---|---|---|---|---|---|---|---|---|
| | baseline | nadir | recovery | baseline | nadir | recovery | baseline | nadir | recovery |
| 1 | 43.29 | 38.22 | 40.17 | 31.43 | 31.8 | 29.96 | 10.62 | 5 | 8.79 |
| 2 | 44.85 | 37.83 | 44.46 | 35.43 | 26.41 | 24.81 | 7.47 | 9.86 | 18.62 |
| 3 | 51.87 | 42.12 | 50.7 | 40.62 | 33.92 | 30.7 | 10.42 | 7.13 | 18.99 |
| 4 | 47.58 | 38.61 | 45.63 | 35.96 | 27.75 | 26.36 | 10.2 | 9.67 | 18.32 |
| 5 | 43.29 | 33.54 | 53.04 | 39.31 | 23.55 | 23.36 | 3.24 | 8.98 | 27.94 |
| 6 | 45.63 | 37.83 | 35.88 | 32.94 | 30.9 | 26.61 | 11.78 | 6.02 | 8.36 |
| 7 | 44.85 | 35.88 | 42.12 | 25.25 | 25.88 | 32.64 | 18.65 | 9.06 | 8.59 |
| 8 | 44.07 | 38.22 | 55.38 | 38.92 | 26.19 | 32.21 | 3.89 | 11.04 | 22.01 |
| 9 | 39.39 | 35.88 | 40.95 | 32.55 | 26.08 | 35.8 | 5.76 | 8.83 | 4.26 |
| 10 | 40.17 | 42.9 | 38.61 | 25.25 | 27.06 | 22.45 | 13.35 | 14.86 | 15.07 |
| 11 | 36.86 | 34.71 | 42.9 | 18.99 | 19.13 | 23.13 | 17.12 | 14.54 | 18.74 |
| 12 | 40.56 | 35.88 | 49.14 | 26.55 | 21.69 | 25.79 | 12.79 | 13.15 | 22.29 |
| 13 | 20.28 | 31.98 | 28.47 | 12.02 | 25.81 | 16.81 | 9.21 | 4.95 | 10.59 |
| 14 | 30.03 | 28.26 | 39.39 | 13.15 | 15.92 | 20.89 | 15.66 | 11.17 | 17.47 |
| 15 | 45.24 | 41.34 | 37.05 | 35.22 | 37.24 | 31.66 | 8.91 | 3 | 4.7 |
| 16 | 40.17 | 33.15 | 32.37 | 24.23 | 20.94 | 22.64 | 4.67 | 11.91 | 8.76 |
| 17 | 41.34 | 39.78 | 41.73 | 33.34 | 34.56 | 22.86 | 7.09 | 4.32 | 42.73 |
| 18 | 40.17 | 38.03 | 38.61 | 31.2 | 27.76 | 31.72 | 8.25 | 9.48 | 6.1 |
| 19 | 39.78 | 39.39 | 45.24 | 33.24 | 23.31 | 29.34 | 5.84 | 14.83 | 15.19 |
| mean ± SEM | 41.02 ± 1.55 | 37.03 ± 0.84 | 42.20 ± 1.55 | 29.77 ± 1.90 | 26.63 ± 1.24 | 26.85 ± 1.13 | 9.73 ± 1.01 | 9.36 ± 0.83 | 15.66 ± 2.14 |

**Table 2:** The baseline, nadir and 6 months post chemotherapy recovery values of ATP (micromoles/deciliter) are shown above for whole blood, red blood cells and the buffy coat for the nineteen evaluable patients.

change from baseline to nadir: 9.73 +/- 1.01 to 9.36 +/- 0.83 (p =0.379; p = 0.344). However, there was a SSIG rise from nadir to recovery: 9.36 +/- 0.83 to 15.66 +/- 2.14 (p = 0.011; p = 0.003). Attempts to find reports of ATP levels on freshly collected and assayed buffy coat specimens were not found by the author on repeated literature searches. Given that a similar pattern was not evident on the red blood cells indicates that this observation is not due to a global effect on the pleuripotent bone marrow stem cells which give rise to both the platelet and erythroid cell lines of production.

## Discussion

Managing Cancer-Related Fatigue (C-RF) is appropriately a therapeutic goal of the oncology community. It is associated with the disease, its treatment or a combination of at least these two factors [3]. This brand of fatigue has been identified at the time of diagnosis in 50-75% of cancer patients. Stasi et al., reported that the prevalence of C-RF increased to 80-96% in patients undergoing chemotherapy and to 60-93% in radiation therapy patients [10]. In women receiving adjuvant chemotherapy for breast carcinoma there was a higher incidence of moderate or severe cognitive impairment in the women undergoing adjuvant chemotherapy as compared to age matched controls (16% vs. 4%; p = 0.008) [11].

Efforts have been made to try to improve C-RF. Energy conservation and activity management has been attempted and produced a modest benefit [12]. With apologies to the authors, this seems like instructing the poor to spend less.

A study utilizing long acting methylphenidate showed no evidence that it improved C-RF over placebo [13]. However, a subset analysis suggested that patients with more severe fatigue demonstrated improvement. Anecdotal experience of the author suggests that regular practice of tai chi chuan helps improve C-RF [4]. Newly published studies are showing benefit but no correlations to ATP levels have been examined [14]. If reduced levels of ATP produce or contribute to C-RF, can we raise them and improve or restore a normal performance score? Doing so would establish a cause and effect relationship between ATP reduction and C-RF.

Chinese tonifying herbs, which possess antioxidant activity, may be candidates as therapeutic interventions. Traditional yang tonifying agents such as Herba Cistanche and Cordyceps have been shown to increase mitochondrial ATP production. On the other hand, yin tonifying herbs such as ganoderma (Reishi) are thought to exert mainly immuno-modulatory functions that may enhance a weak immune system but would not necessarily be expected to improve the performance status of a weakened patient [15]. Li et al., have shown that Panax ginseng, which has been used as a qi invigorating herbal medicine, increases the levels of ATP in mouse liver cells and skeletal muscle cells apparently by inhibiting mitochondrial swelling [16]. Such herbs are appealing candidates for future clinical studies to explore the hypothesis that C-RF is at least in part due to decreased blood ATP levels.

Our data show that whole blood and red blood cell ATP levels decline in patients who receive limited term chemotherapy. The deficiencies substantially auto correct in 6 month's time. However, unless one can demonstrate that C-RF can be mitigated or reversed more quickly by restoring low blood ATP levels, a cause and effect relationship between them remains speculative.

Defects in cellular immunity associated with underlying malignancy have been richly described in the medical literature. Our finding, in the buffy coat fraction, that baseline and nadir ATP levels were equivalent but rose after 6 months is noteworthy but unexplained at this

time. They suggest that there may exist a metabolic deficiency in the white blood cell fraction in persons at the time of diagnosis with the malignancies in our study group (carcinoma of the breast, colon, lung, ovary and lymphoma). This deficiency may be due to a transient metabolic defect involving reduced ATP production. Mitigation of this deficiency could potentially hasten restoration of cellular immunity. The finding that red blood cell ATP did not fully recover by 6 months after completion of the treatments raises the question of whether the deficit is permanent or may require a longer time for recovery?

## Conclusion

Cancer related fatigue is a significant problem for patients diagnosed with cancer which can be exacerbated by chemotherapy and/or radiation therapy. We have shown that patients undergoing limited courses of chemotherapy experience SSIG reductions in whole blood and red blood cell ATP levels. A rise in buffy coat ATP levels after nadir to a level higher than pretreatment baseline was identified but remains unexplained. Our observations may be the underlying biochemical explanation for C-RF. Doing so could possibly ameliorate the lives of the millions of cancer patients around the world. Based on our experience, future acupuncture investigators evaluating the effects of acupuncture on fatigue within specific disease states ought to consider measuring blood ATP levels as a parameter. Additional studies are indicated.

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## Conflict of Interest Statement

No conflict of interest existed. The funds for this research were donations from patients and their families. No commercial interests were involved with this project.

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