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Reactive oxygen species, antioxidant mechanisms, and serum cytokine levels in cancer patients: impact of an antioxidant treatment.

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OBJECTIVE: It has not been well established whether the oxidative stress found in cancer patients results from an increased production of oxidants in the body or from a failure of physiological antioxidant systems. To further investigate this question, we have assessed the blood levels of reactive oxygen species as a marker of free radicals producing oxidative stress and the most relevant of the physiological body enzymes counteracting reactive oxygen species, namely glutathione peroxidase and superoxide dismutase. We also investigated serum levels of proinflammatory cytokines and IL-2. All of these parameters were studied in relation to the most important clinical index of disease progression--namely, the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS). We also tested the reducing ability of different antioxidant agents on reactive oxygen species levels by measuring the increase in glutathione peroxidase activity and the reduction of serum levels of IL-6 and TNF-alpha. **PATIENTS AND METHODS:** We carried out an open nonrandomized study on 28 advanced stage cancer patients (stage III, 10.7% and stage IV, 89.3%) with tumors at different sites. The patients were divided into 5 groups, and a different antioxidant treatment was administered to each group. The antioxidants were alpha lipoic acid 200 mg/day orally; N-acetylcysteine 1800 mg/day i.v. or carboxycysteine-lysine salt 2.7 g/day orally; amifostine 375 mg/day i.v.; reduced glutathione 600 mg/day i.v.; and a combination of vitamin A 30,000 IU/day orally, vitamin E 70 mg/day orally, and vitamin C 500 mg/day orally. The antioxidant treatment was administered for 10 consecutive days. **RESULTS:** We found that all but one of the antioxidants tested were effective in reducing reactive oxygen species levels, and two of them (cysteine-containing compounds and

amifostine) had the additional effect of increasing glutathione peroxidase activity. Comprehensively, the antioxidant treatment was found to have an effect on both reactive oxygen species levels and glutathione peroxidase activity. The antioxidant treatment also reduced the serum levels of IL-6 and TNF-alpha. Patients in both ECOG PS 0-1 and ECOG PS 2-3 responded to antioxidant treatment.

J Cell Physiol. 2003 Mar; 194(3): 325-40.

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Alpha-lipoic acid induces p27Kip-dependent cell cycle arrest in non-transformed cell lines and apoptosis in tumor cell lines.

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alpha-Lipoic acid is a naturally-occurring co-factor found in a number of multi-enzyme complexes regulating metabolism. We report here that alpha-lipoic acid induces hyperacetylation of histones in vivo and has differential effects on the growth and viability of normal versus transformed cell lines. The human tumor cell lines FaDu and Jurkat, as well as a Ki-v-Ras-transformed Balb/c-3T3 murine mesenchymal cell line, all initiated apoptosis following exposure to alpha-lipoic acid. In contrast, treatment of non-transformed cell lines with alpha-lipoic acid resulted only in reversible cell cycle arrest in G0/G1. Treatment with butyrate, another short-chain fatty acid, induced a G0/G1 arrest in both transformed and non-transformed cell lines. alpha-Lipoic acid caused a post-translational elevation in the levels of the cyclin-dependent kinase inhibitor p27Kip1. Studies using p27Kip1-deficient MEF cells demonstrated that p27Kip1 was required for the alpha-lipoic acid-mediated cell cycle arrest. The mechanism of apoptosis was independent of Fas-mediated signaling, as alpha-lipoic acid-treated Jurkat cell mutants deficient in Fas or FADD retained sensitivity to apoptosis. The differential selectivity of the pro-apoptotic effects of alpha-lipoic acid for transformed cells supports its potential use in the treatment of neoplastic disorders.

Klin Wochenschr. 1991 Oct 2;69(15): 722-4.

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Alpha-lipoic acid is an effective inhibitor of human immuno-deficiency virus (HIV-1) replication.

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Alpha-lipoic acid, a naturally occurring disulfide-compound that acts as a cellular coenzyme, inhibits replication of HIV-1 in cultured lymphoid T-cells. Alpha-lipoic acid was added 16 hours after infection of the T-cell lines Jurkat, SupT1 and Molt-4 with HTLV IIIB and HIV-1 Wal (a wild type HIV-1 isolate). We observed a dose dependent inhibition of HIV-1-replication in CPE (Cytopathic effect) formation, reverse transcriptase activity and plaque formation on CD4-transformed HeLa-cells. An over

90% reduction of reverse transcriptase activity could be achieved with 70 micrograms alpha-lipoic acid/ml, a complete reduction of plaque-forming units at concentrations of greater than or equal to 35 micrograms alpha-lipoic acid/ml. An augmentation of the antiviral activity was seen by combination of zidovudine and low dose of alpha-lipoic acid (7 micrograms/ml). Trypan blue staining revealed no toxic effects of alpha-lipoic acids on peripheral blood mono-nuclear cells and T-cell lines even in concentrations of greater than or equal to 70 micrograms/ml. Therefore, we propose the inclusion of alpha-lipoic acid into chemotherapy trials in combination with zidovudine.

Arzneimittelforschung. 1992 Jun; 42(6): 829-31.

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Influence of alpha-lipoic acid on intracellular glutathione in vitro and in vivo.

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The influence of alpha-lipoic acid (CAS 62-46-4) on the amount of intracellular glutathione (GSH) was investigated in vitro and in vivo. Using murine neuroblastoma as well as melanoma cell lines in vitro, a dose-dependent increase of GSH content was observed. Dependent on the source of tumor cells the increase was 30-70% compared to untreated controls. Normal lung tissue of mice also revealed about 50% increase in glutathione upon treatment with lipoic acid. This corresponds with protection from irradiation damage in these in vitro studies. Survival rate of irradiated murine neuroblastoma was increased at doses of 100 micrograms lipoic acid/d from 2% to about 10%. In agreement with the in vitro studies, in vivo experiments with whole body irradiation (5 and 8 Gy) in mice revealed that the number of surviving animals was doubled at a dose of 16 mg lipoic acid/kg. Improvement of cell viability and irradiation protection by the physiological compound lipoic acid runs parallel with an increase of intracellular GSH/GSSG ratio.