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Commentary Open Access

Biochemical and Pharmacological Effects of Mitoxantrone and Acetyl-L-Carnitine in Mice with a Solid Form of Ehrlich Tumour

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Commentary

Since the beginning of 1990, our Laboratories begun a series of in vivo experimental studies to evaluate the effect of carnitine derivatives on the antineoplastic activity of mitoxantrone (MX) a dihydroxy-anthracene derivative on various animal models of cancer The objective was to determine pre-clinically whether carnitine and its acyl-derivatives in combination with mitoxantrone could be found to be good candidates to ameliorate host's metabolic response to tumour processes, and therefore could play a valuable role in the field of cancer treatment.

Despite significant advances in the chemotherapeutic treatments of neoplastic diseases, success in the treatment of many solid tumours has been limited [1]. Drug toxicity [2] and resistance development during therapy remain the 2 principal reasons for treatment failure in a great majority of patients with metastatic cancer [3-5]. Chemotherapy is the major therapeutic approaches in several human life-threatening diseases including microbial infections, autoimmune diseases and cancers [6] and drug combinations are the key to most cancer treatments [7-8] Thus, the development of successful approaches to treat cancer will require combinations of drugs and/or treatment modalities to optimize the tumour response to therapy whilst modulating the harmful side effects. One approach is to develop a rational combination of cytostatic drugs and agents that modulate the drugs' chemotherapeutic activity and toxicological profile.

The presence of cancer appears to cause metabolic alterations in the host [9]. In addition to this, a number of studies have demonstrated that anticancer therapy also can induce modifications in metabolism normally mediated by the carnitine system of mitochondria [10]. Dysfunction of the carnitine system in non-tumour tissue following anticancer therapy has been reported. In this setting, supplementation with carnitine derivatives might increase the general metabolic activity of normal cells so that they might better withstand the adverse effects of chemotherapy aimed at tumour cells.

Our hypothesis was that, supplementation with carnitine derivatives may provide a safe and effective means of enhancing the response to chemotherapy and reducing or preventing side effects.

The role of the carnitine system in cell metabolism is mainly known in mitochondria where the interaction between fatty acid and glucose metabolism is fundamental for cell energy production [11-12]. This is the biochemical basis of our hypothesis. Acetyl-L-carnitine (ALC) is widely available as a food supplement and has been reported to play a relevant role in energy metabolism and stress response, because its function in the complex metabolic system regulating the acetyl-CoA levels which provide a source of acetyl groups for metabolic and acetylation-regulated processes [13].

Mitoxantrone (MX), an anthracenedione with a broad spectrum of antitumor activity, is used in the treatment of breast and prostate cancer, acute leukemia, and lymphomas, and since 2000 it has been approved by the U.S Food and Drug Administration (FDA) as an immunomodulatory agent for reducing the neurological disability of worsening relapsing-remitting multiple sclerosis [14]. Many studies have reported the cardiotoxicity of MX [15], although the underlying mechanisms are still poorly understood.

We previously reported [16] that acetyl carnitine has a mitigating effect on mitoxantrone (MX) toxicity and that it helped to prolong the survival of mice with the ascetic form of leukemia L1210. In this study commented here, we investigated the effect of acetyl-L-Carnitine (ALC) alone and in combination with the antineoplastic agent mitoxantrone (MX) in animal bearing the solid form of Ehrlich tumour (STE).

Note that the experiments were designed and conducted in accordance with European Union recommendations on handling of experimental animals and were approved by the ethical commission of Charles University in the Czech Republic.

Our results show that mice treated with MX alone at 6 mg kg^{-1} lived significantly longer than both untreated STE controls and mice given both MX (6 mg kg^{-1}) and (ALC 200 mg kg^{-1}) together. MX monotherapy (iv) at this dose produced a mean survival of 24.73 days (95% CI 19.49-31.39), about 38.8% longer than the mean survival of untreated STE animals. Doses greater than 6 mg kg^{1} of MX (9 or 12 mg kg^{-1}) were more toxic to the animals, as documented by the decrease in survival time. Those higher doses, however, were associated with greater inhibitory effect on the growth of STE. Repeated doses of ALC alone were beneficial and produced a mean survival of 28.26 days (95% CI 19.21-41.57), about 58.8% longer than the untreated STE control group (17.81 days) [17]. Signs of toxicity in our experiments included decreased body weight gain and body weight loss. The significant reductions in body weight gain and progressive weight loss observed in the MX and MX-ALC treatment groups 14 days after inoculation of STE were due to reduced food intake (data not shown). This weight loss was primarily an effect of the chemotherapy treatment rather than the tumour per se. The significant change in the relative weight of the liver that was observed in the present study could be a result of MX-induced injury of hepatic cells, which may explain the cytotoxicity of MX at higher doses. Higher concentrations of MX are known to inhibit DNA and protein synthesis; indeed, marked growth

inhibition of the tumours was noted. MX-related serum biochemistry changes consisted of a decrease in serum total protein; serum albumin and bilirubin remained unchanged.

Histological evaluation of organs in mice treated with MX alone showed changes mainly in the liver. The fact that fewer metastases were observed in the MX-treated groups accounts for the tumour cytotoxicity and cytostatic effect of MX. Our histological findings revealed that at the lowest dose of MX tested (6 mg kg^{-1}), small metastases appeared in liver parenchyma. At higher doses of MX (9 and 12 mg kg^{-1}) the number of metastases was reduced and the tumours were smaller in size. At MX 12 mg kg^{-1} there was a significant reduction in tumour weight of treated animals and also a reduction in the length of survival. At higher dose, the combination of MX and ALC induced significant alterations to hepatic and organ (lungs, kidneys heart, mediastinum) histology, which would likely have serious implications for the health of treated animals. However, contrary to our hypothesis that ALC would improve therapeutic outcomes of MX therapy, the histological findings indicate that ALC is inappropriate to combine with MX in the treatment of STE at higher dose design.

In conclusion, the protective effect of ALC in combination therapy with the cytostatic drug MX was not supported in this study by our findings that the agent did not improve the therapeutic outcomes of MX therapy.

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