EFFECT OF ACETYL-L-CARNITINE ON LEUKEMIA L1210 RESISTANT TO MITOXANTRONE

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Summary: Supportive care in tumour chemotherapy is a subject of intensive research. The complications of cytostatic therapy are a cause of extensive research of their pharmacological interactions and side effects. The immunologic and biochemical changes accompanying tumours are the factor that is most responsible for the worsening of the physiology of the host. Regimens containing carnitine and its acetyl-derivative are used in many cases, among others even for preventing hepatotoxicity. Our hypothesis was to verify the supporting metabolic effects of acetyl-L-carnitine hydrochloride (ALC) in combined therapy with mitoxantrone (MX) and hepatotoxic cytostatic drugs including alkylating agents. This present report describes the effect of ALC in combination with MX on DBA/2 male mice bearing a transplantable L1210 leukemia resistant to MX. The criterion for evaluation of effect was the length of survival time of experimental animals. The proportional-hazards model quadratic in the drug dose (7) was used for survival time evaluation and optimal dose calculation. The hazard functions and the index of relative hazard were determined using Weibull distribution after logarithmic transformation of the entered data in each particular group. The dose-response curve was represented by a second-degree polynomial without absolute term. The combination therapy revealed that the optimal dose of ALC was 186 mg/kg s.c. This relation is shown in Fig.1. A significant effect of ALC (s.c.) in combined therapy with MX (6 mg/kg i.v.) given to animals bearing an experimental form of leukemia L1210/MX resistant to MX was proven at a level of probability p ≤ 0.001. The effect of ALC in monotherapy was not demonstrable.

Key words: Mitoxantrone dihydrochloride (MX); Acetyl-L-carnitine hydrochloride (ALC); Protective effect and L1210 leukemia

Introduction

Mitoxantrone dihydrochloride, a synthetic anthraquinone, is a potent antineoplastic agent and active substance of REFADOR Inj. PLIVA-LACHEMA. The chemical structure and chemical name are:

![Chemical structure of Mitoxantrone dihydrochloride](image.png)

1,4-dihydroxy-5,8-bis(2-(2-hydroxyethyl)aminojethylamino)anthracene 9,10-dione dihydrochloride.

This active component of the preparation is manufactured by the Research Institute of Organic Synthesis (VÚOS) (17) Pardubice, Czech Republic.

Mitoxantrone (MX) can be used alone and in combination with other agents against various types of neoplasias, including solid tumours (8) and haematological malignancies (6,21). Toxic effects of anticancer therapeutics and acquired cell resistance to these agents, occurring in the course of therapy, are the limiting factors of successful cancer treatment (14,20).

Among substances used to give metabolic support, were trying pre-clinically to determine whether some L-carnitine derivatives, in combination with MX could ameliorate host's metabolic response to tumour processes. The aim was to document new possibilities of using a combination of chemotherapeutics with substances that modulate their therapeutic and toxicologic profiles and that could be of clinical importance as new antitumour drugs and new therapeutic protocols.

In this work we investigated the therapeutic benefit of acetyl-L-carnitine (ALC) in combination with MX on a murine leukemia L1210 resistant to MX.

Materials and methods

Mitoxantrone (batch No 12/309 VÚOS) was purchased from the Research Institute of Pharmacy and Biochemistry...