Biochemical Control of High-Dose Methotrexate/Leucovorin Rescue Therapy

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Summary

High-dose methotrexate/Leucovorin rescue therapy is based on the assumption of differences in the transport system for folate compounds between normal and malignant proliferating cells. Thus, under normal conditions, methotrexate (MTX) and Leucovorin (citrovorum factor, CF) in low doses can enter the cells by an active transport system, whereas in some malignancies – such as osteosarcoma – these substances only penetrate through the cell membrane by passive diffusion if they are given in very high doses. Therefore, after high-dose MTX treatment, the cytotoxic effect of the folate antagonist is compensated for by rescue with Leucovorin in low doses only in the normal cell system. The consequence of this kind of treatment is a selective antitumor effect.

To avoid cytotoxic side effects, this therapeutic regimen must be monitored carefully. The decrease of the ratio of $^3$H-deoxyuridine ($dUR$)/$^3$H-thymidine ($dTR$) incorporation into the DNA of the cells is a good biochemical parameter for estimating the MTX effect on rapidly proliferating cell systems. Using this indicator, it was shown that the usually administered dose of Leucovorin is not sufficient for an effective rescue of the bone marrow cells as long as the MTX serum concentration is equal or higher than $10^{-6}M$. If in critical cases the MTX elimination is retarded, a rescue can only be achieved by Leucovorin at doses tenfold higher than the actual amount of MTX in the whole body system. The Leucovorin rescue doses under such circumstances can be calculated according to the formula

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\text{Leucovorin (mg)} = 10 \times \text{MTX (mg/l)} \times 0.76 \times \text{body weight (kg)}.
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Introduction

High-dose methotrexate (HDMTX) therapy followed by Leucovorin (citrovorum factor, CF) rescue is based on the assumption that primary resistant tumors have an impaired active membrane transport system for folate compounds which is normally shared by methotrexate (MTX) (Fig. 1). At very high MTX serum concentrations, however, the drug can enter these cells by passive diffusion independent of the active transport system.
**Fig. 1.** Principle of high-dose methotrexate (HDMTX) therapy

**Fig. 2.** Biochemical effects of methotrexate (MTX)

1. Inhibition of dihydrofolate reductase
2. Reduced $C_1$ pool → substrate deficiency in thymidylate synthesis
   → decreased dUR incorporation into DNA
3. Increased thymidine kinase activity
   → salvage pathway
   → increased dTR incorporation into DNA