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Cancer Chemotherapy and Pharmacology

Letter to the Editor

Dear Sir:

We would like to point out some data related to MTX metabolism in blood to supplement that presented in two recent articles in Cancer Chemotherapy and Pharmacology [5, 6]. When these articles were submitted for publication, several papers had already been published which confirm and expand upon the results and hypothesis presented in these articles.

In 1981 da Costa and Iqbal [1] demonstrated a linear uptake of plasma MTX into erythrocytes up to a concentration of 10^{-3} M and also noted the same biphasic decline and rise of red cell MTX seen by Schalhorn et al. [5]. Both Schalhorn [5] and Steele [6] speculated that developing red cells in the marrow take up MTX and form polyglutamates. Therefore, the increase in red cell MTX was due to the maturation and release of the progenitor cells into the circulation. This was also theorized by da Costa.

Schalhorn found MTX polyglutamates in red cells 1 week after a dose of MTX. Steele was unable to analyze polyglutamates. In 1981 Kamen et al. [2] demonstrated MTX polyglutamates in human red cells with Sephadex G-15 chromatography. More than 60% of the MTX in these cells was polyglutamylated. Krakower et al. [3] also documented MTX polyglutamates in the red cells of children with acute lymphocytic leukemia who had been receiving weekly intramuscular methotrexate (20 mg/m^2). Polyglutamates up to MTX(glu)$_6$ were detected using HPLC. More recently we have detected MTX(glu)$_7$ in red cells of rats which received a single intraperitoneal injection of 50 mg MTX/m^2. After 1 week less than one-third of the red cell MTX was unconjugated, and levels of MTX polyglutamates remained constant. As a result the percentages of total erythrocyte MTX existing as polyglutamates increased to 56 ± 20% (four animals). The subsequent decline of blood MTX seemed to follow the erythrocyte life span [4]. In summary, data had already been published to support the theory advanced by Schalhorn and Steele.

Sincerely,

Glenn R. Krakower, Ph.D.

Barton A. Kamen, M. D., Ph.D.,
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and Pharmacology and Toxicology

References

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2. Kamen BA, Nylen PA, Camitta BM, Bertino JR (1981) Methotrexate accumulation and folate depletion in cells as a possible mechanism of chronic toxicity to the drug. Br J Haematol 49: 355
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5. Schalhorn A, Sauer H, Wilmanns W, Stupp-Poutot G (1982) Pharmacokinetics of erythrocyte methotrexate after high-dose methotrexate. Cancer Chemother Pharmacol 9: 65
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Dear Sir:

We noticed the letter of Dr. Krakower and Dr. Kamen with great interest. The articles of Kamen et al. in Brit. J. Haematol. and da Costa et al. in Cancer appeared in November and December 1981, respectively. At that time our paper on the pharmacokinetics of erythrocyte methotrexate after high-dose methotrexate was already submitted for publication in CCP. Therefore the results of the above mentioned articles as well as the paper Krakower published in 1982 in Anal. Biochem. could not be considered in the discussion of our paper. As only minor details of our article had to be changed before the second submission, we cannot understand why the date of submission in the finally printed expedition is March 17, 1982.

In the meantime we were able to determine the half-life of MTX and MTX polyglutamates in erythrocytes of different patients undergoing high-dose methotrexate therapy. Though the half-life of both unchanged MTX and MTX polyglutamates differed considerably, in each case MTX polyglutamates disappeared much more slowly than unchanged MTX, results which are in agreement with those published by Krakower and Kamen.

A typical course of erythrocyte MTX in a patient with metastatic leiomyosarcoma is illustrated in Fig. 1: Six weeks after the antecedent high-dose MTX therapy only MTX polyglutamates were detectable. Three days after the 21st HDMTX infusion both MTX polyglutamates and unchanged MTX started to increase again and to reach maximum values on day 13. Thereafter MTX fell rather quickly with a half-life of 8 days whereas the MTX polyglutamates declined very slowly; their half-life was 32 days. Though on day 13 the concentration of MTX yet surpassed that of MTX polyglutamates, 6 weeks after this HDMTX therapy no unchanged MTX but only MTX polyglutamates were detected in the erythrocytes.

Sincerely,

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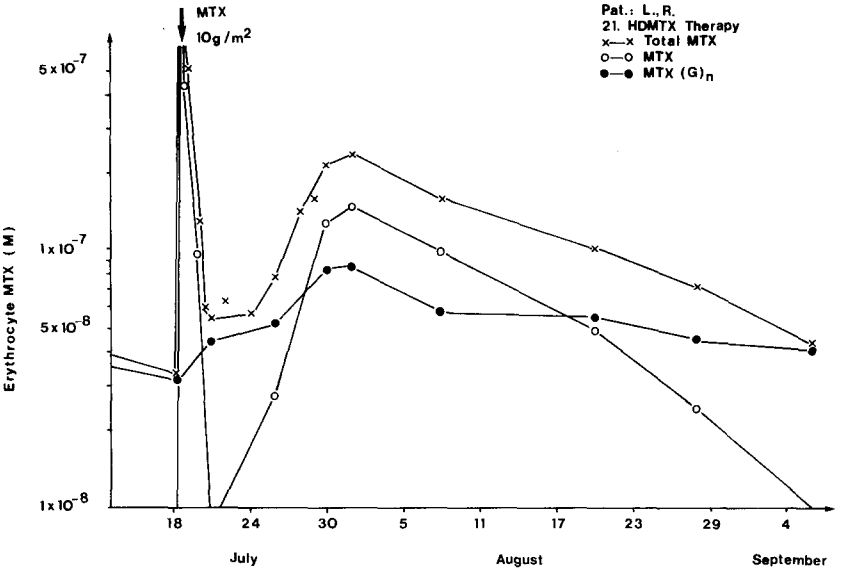

Fig. 1. Kinetics of erythrocyte MTX after the 21st HDMTX infusion in a patient with metastatic leiomyosarcoma