CANCER AND CHEMOTHERAPY

Volume III

Antineoplastic Agents

Edited by

Stanley T. Crooke

Research and Development
Smith Kline & French Laboratories
Philadelphia, Pennsylvania
and
Department of Pharmacology
Baylor College of Medicine
Texas Medical Center
Houston, Texas

Archie W. Prestayko

Research and Development
Bristol Laboratories
Syracuse, New York
and
Department of Pharmacology
Baylor College of Medicine
Texas Medical Center
Houston, Texas

Editorial Assistant

Nancy Alder

1981

ACADEMIC PRESS
A Subsidiary of Harcourt Brace Jovanovich, Publishers
New York London Toronto Sydney San Francisco

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

Library of Congress Cataloging in Publication Data
Main entry under title:

Cancer and chemotherapy.

Includes bibliographies and index.
CONTENTS: v. 1. Introduction to neoplasia and antineoplastic chemotherapy--v. 2. Introduction to clinical oncology--v. 3. Antineoplastic agents.
1. Cancer--Chemotherapy. 2. Antineoplastic agents. I. Crooke, Stanley T. II. Prestayko, Archie W. [DNLM: 1. Neoplasms--Drug therapy. 2. Antineoplastic agents. QZ267.C214]
RC667.C28 616.99'4061 79-8536
ISBN 0-12-197803-6 (v. 3)

PRINTED IN THE UNITED STATES OF AMERICA

81 82 83 84 9 8 7 6 5 4 3 2 1

22

METHOTREXATE: CLINICAL PHARMACOLOGY AND THERAPEUTIC APPLICATION

J. R. Bertino

I. INTRODUCTION

Methotrexate (MTX) continues to be a valuable drug for the treatment of human neoplastic disease. Attempts to increase its efficacy over the years since its introduction into the clinic in 1948 (Farber *et al.*, 1948) have involved evaluation of various dosage schedules, as well as its use in combination with other drugs (Bertino, 1979). Doses have escalated from 1–5 mg/m² per day to very high doses (1–20 gm/m²), followed by leucovorin (LV, N^{10}-formyltetrahydrofolate) ''rescue'' (Bertino, 1977). The use of MTX in these high doses has led to a reexamination of the clinical pharmacology of this drug in an attempt to prevent serious drug toxicity. This chapter will discuss the clinical

CANCER AND CHEMOTHERAPY, VOL. III

ISBN 0-12-197803-6

pharmacology and clinical application of MTX, with emphasis on high-dose regimens.*

II. PHARMACOLOGY

A. Mechanism of Action†

The biochemical event that leads to cell death following MTX administration appears to be powerful, and in certain circumstances (pH 6.0), ''stoichiometric,'' inhibition of the enzyme dihydrofolate reductase (DHFR) (Werkheiser 1961; Bertino, 1963; Bertino *et al.,* 1964). Inhibition of this enzyme activity leads to decreased tetrahydrofolate formation, and consequent inhibition of thymidylate and purine biosynthesis (Johns and Bertino, 1974; Chabner and Johns, 1977) (see Fig. 3, Bertino, Chapter 18, this volume). Therefore cells undergoing DNA synthesis during the S phase of the cell cycle are susceptible to MTX, and this drug acts primarily on cells undergoing rapid growth (Bruce *et al.,* 1966; Hryniuk *et al.,* 1969).

In leukemia cells, MTX appears to be transported by an active, carrier-mediated transport system, utilized by the naturally occurring folates, leucovorin (5-formyltetrahydrofolate, LV) and 5-methyltetrahydrofolate (Nahas *et al.,* 1972; Goldman *et al.,* 1968, 1971; Bender, 1975). Folic acid, which is poorly transported, apparently does not use this system (Nahas *et al.,* 1972; Huennekens *et al.,* 1978). MTX, therefore, also acts to compete with reduced folates for transport into cells. MTX also acts to facilitate efflux of reduced folates from cells, thus adding to the relative folate ''starvation'' caused by impairment of reduced folate transport. Thus MTX not only prevents reduced folate resynthesis by inhibiting DHFR, but also in high concentration inhibits influx of folates and stimulates efflux of reduced folates (Goldman, 1971).

B. Absorption

Methotrexate is a relatively polar, weak dicarboxylic acid (the pK_as of the glutamate carboxyl groups are 4.8 and 5.5) (Seegar *et al.,* 1949; Liegler *et al.,* 1969). In doses of up to 30 mg/m² the absorption is almost complete (Henderson *et al.,* 1965; Huffman *et al.,* 1973). Peak blood levels are reached in 1–2 hr when the patient is in the fasting state. As doses exceed 30 mg/m², proportionally less drug is absorbed (Henderson *et al.,* 1965; Wan *et al.,* 1974), and high-dose regimens are administered via the intravenous route. MTX can also be administered S.C., I.M., or I.P.; peak blood levels are rapidly achieved in 15–30 min.

*For other recent reviews, see Bertino (1977), Chabner and Johns (1977), and Bleyer (1978).

† For a more detailed description of the chemistry and mechanism of action of this drug see chapter 18, this volume.

The drug can also be administered intrathecally; in this circumstance the drug slowly leaks out of the cerebrospinal fluid (CSF) and plasma levels are maintained for two to three times longer than would be expected after intravenous administration (Jacobs *et al.*, 1975b). Thus there is more potential for systematic toxicity after intrathecal administration than after a given dose administered parenterally (Jacobs *et al.*, 1975b; Cadman *et al.*, 1976).

C. Plasma Disappearance and Distribution

After intravenous administration, plasma half-life values have been measured, and a triphasic curve has been described (Huffman *et al.*, 1973; Stoller *et al.*, 1975). The initial half-life lasts about 0.75 hr and reflects the distribution phase. Calculations of the volumes of distribution indicate that the drug is distributed initially in the extracellular space and then in total body water (Leme *et al.*, 1975; Henderson *et al.*, 1965). A second phase ($t_{\frac{1}{2}}$ = 2–3 hr) can also be identified, which probably reflects the renal clearance of the drug (Isacoff *et al.*, 1976, 1977). A terminal phase can also be measured when plasma levels decrease below 10^{-7} *M* (24–48 hr after high-dose therapy) (Stoller *et al.*, 1975). This phase has a half-life of 10 hr and may be the result of enterohepatic circulation of the drug. Toxic effects of MTX may be the result of this prolonged third phase, since DNA synthesis in replicating tissues may be inhibited until plasma levels fall below 10^{-8} (Chabner and Young, 1973). Experiments in mice in which this terminal phase is eliminated by carboxypeptidase G_1, an MTX-degrading enzyme, have demonstrated that much of the toxicity of MTX is relieved (Chabner *et al.*, 1972).

Distribution of MTX into the CSF, peritoneal, and pleural cavities occurs slowly. In the presence of pleural or peritoneal effusions, these "third" spaces may act as reservoirs and prolong plasma MTX disappearance with an increase in systemic toxicity (Creavan *et al.*, 1973; Tattersall *et al.*, 1975). When large doses of MTX are used (>500 mg/m^2), high CSF levels are achieved ($>10^{-6}$ *M*) (Shapiro *et al.*, 1975; Tattersall *et al.*, 1975b). Presumably, these CSF levels are the result of the high plasma levels (10^{-3} *M*) and reflect a small amount of unchanged drug that penetrates this barrier.

Organ distribution of MTX appears to reflect the presence or absence of specific transport mechanisms, as well as the levels of DHFR present in the cells, and perhaps the amount of conversion to oligoglutamates (Whitehead *et al.*, 1975). The organs that contain the highest levels of MTX and retain it for the longer periods of time are the liver and kidney (Charache *et al.*, 1960; Anderson *et al.*, 1970). A study utilized ^{131}I-labeled aminopterin showed that these organs rapidly took up this folate analogue and retained it for long periods of time (Johns *et al.*, 1968). Until recently it was believed on the basis of displacement of tissue folates into the urine, and characterization of the inhibitor by chromatography and by enzyme inhibition, that the material bound in tissues was unchanged

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.