Folate Antagonists as Therapeutic Agents

2

Pharmacology, Experimental and Clinical Therapeutics

Edited by

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VOLUME 2

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Preface

It is apparent that folate antagonists have now assumed major importance in the treatment of a variety of human disorders. Their use derives from the large number of conceptual advances made over the past three decades in our knowledge of folate metabolism and its role in macromolecular synthesis and the subsequent discovery of a number of agents that selectively antagonize this metabolism in target cell populations. In view of this progress, it seemed highly desirable to bring together the vast literature on this topic in the form of a cohesive and comprehensive treatise.

Advances in our knowledge of folate metabolism and its antagonism over the years have relied upon studies in both microbial and mammalian systems with cumulative impact, not only on the treatment of diseases of microbial origin, but also on the treatment of proliferative disorders, namely cancer and psoriasis. Therefore, we sought to organize these volumes according to the various disciplines from which contributions have originated rather than in a disease-oriented manner. In this way we believe we have more effectively integrated the important concepts that have arisen from a highly diverse group of studies in different experimental systems. Accordingly, in Volume 1 we included chapters dealing with molecular aspects of the enzymology and regulation of the metabolism of folate compounds, the mode of action of various categories of folate antagonists, approaches to their synthetic design and membrane transport, and acquired resistance. In Volume 2, chapters are included that focus on the net biochemical and cytotoxic effects of folate antagonists, probable bases for their selectivity, and the consequence of their interaction with other antimetabolites. The remaining chapters deal with the broad range of pharmacological and therapeutic properties of the various folate antagonists in experimental animal models and in patients.

In organizing the format for these volumes we have attempted to develop a balanced and comprehensive view of active research in the various areas covered. As such, we hope that these volumes will provide an authoritative reference

source and prove to be of value to laboratory and clinical investigators in the field of chemotherapy. We also hope that the broad range of coverage provided will be of interest to students, researchers, and medical practitioners in the fields of infectious, tropical, and psoriatic disease and oncology.

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Introduction

Folate metabolism represents an attractive target for chemotherapy, since it plays a key role in the biosynthesis of nucleic acid precursors. It is of interest, therefore, to note that in the less than four decades since the identification of folic acid as a vitamin, agents that antagonize its metabolic role have been discovered that are effective, not only against proliferative disorders such as cancer and psoriasis, but also against a variety of microbial diseases. This area of chemotherapy is also unique in that inhibitory effects of folate antagonists on a single target, dihydrofolate reductase, can impact macromolecular biosynthesis and cytotoxicity at a number of metabolic steps involving folate-dependent biosynthetic reactions. However, as documented in various chapters of these volumes, it is now becoming clear that direct effects on the folate-dependent reactions themselves may account for a good measure of the total antifolate effect observed in some target cells under certain circumstances.

The penultimate question pertaining to any chemotherapeutic strategy relates to the manner in which adequate therapeutic selectivity can be achieved. This is realized in the case of bacterial and plasmodial disease by a rare example of differential inhibition by "small-molecule" antifolates of the primary enzyme target, dihydrofolate reductase. The basis of selectivity during therapy of neoplastic disease with antifolates, when obtained, may actually be derived on a multifactoral level, including sites unrelated to this primary enzyme target. Evidence is discussed in these volumes for an emerging role of mediated membrane transport and intracellular metabolic disposition in the form of polyglutamylation. To what extent additional metabolic factors may contribute should become clear in the not-too-distant future.

From an examination of the documentation provided in these volumes, it is apparent that significant advances have been made in the use of folate antagonists for the treatment of a number of human diseases. It is also clear that advances will continue to be made in a number of these clinical areas. To a large measure these advances derive from the vast amount of information now available as to the biochemical and pharmacological actions of these agents. These data have

provided much needed direction for new drug design. With this impetus, improved methods of chemical synthesis have brought forth a number of new agents with exciting potential for more effective clinical application. Finally, a review of the wealth of information provided in these volumes makes it eminently clear that progress made in this area of therapeutic research will provide a useful model for similar efforts toward more rational drug design with other categories of agents, particularly in the area of neoplastic disease. It is our hope that the coverage provided will serve investigators in this and related fields who continue to strive for more improved chemotherapy of human disease. Finally, the editors gratefully acknowledge their indebtedness to the many contributors who made the publication of these volumes possible.

F. M. Sirotnak

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CHAPTER ONE

Experimental Cancer Chemotherapy with Folate Antagonists

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I. History and Development of Methotrexate

The present-day prominent position of chemotherapy in the field of cancer management owes much to the continuous and sustained research on an inordinate number of folic acid antagonists.

The development of folate analogs as useful anticancer drugs has been an interesting and exciting story in the biomedical world. The notion that certain types of cancer, especially leukemias, might be nutritional deficiency diseases related to various types of anemia sparked the initiation of a few experiments in the latter part of the 1930s through 1940. This was a time of revolutionary discoveries in the field of nutrition, especially in relation to metabolites, and concurrently in the field of chemotherapy, mainly directed toward antimicrobial agents. Those pre-World War II days were filled with excitement over the ultimate goal of developing or discovering the magic bullet for infectious diseases and ultimately for cancer.

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The initial observations of Lewisohn, Laszlo, and the Leuchtenbergers (reported in 1947) that extracts of barley and yeast, folic acid concentrate, *Lactobacillus casei* factor, and other natural materials produced tumor inhibition in both spontaneous and transplanted mouse tumors certainly created the atmosphere for intensive research on growth factors and antigrowth factors. Even though the reports by the Mt. Sinai group were of great interest, it must be recalled that confirmation of their experiments was not forthcoming. In fact, Sugiura, under the supervision of Cornelius P. Rhoads and with the assistance of a technician from Lewisohn's laboratory, was unable to confirm any of the results, and in a classic presentation from Memorial Hospital on 2 August 1945 Dr. Sugiura stated, "It is concluded that the use of yeast and barley extracts and *L. casei* 'fermentation factor' in the treatment of mice bearing sarcoma 180, or spontaneous mammary adenocarcinomas, produced neither an inhibitory nor a curative effect upon these tumors" (Sugiura, 1947, p. 212).

These early controversial studies paved the way for clinical trials of folate-like conjugates, for example, teropterin, which reportedly reduced the cancer-related pain of patients and possibly decreased white blood cell counts (Farber *et al.*, 1947). The mechanisms of these biological activities by a natural growth factor have never been explained; indeed, one might conclude that a "toxic" impurity was present in the preparations. The puzzling data were stimuli to many, but especially to the investigators at laboratories of the American Cyanamid Company, who initiated an aggressive program in folate and antifolate chemistry and biology in 1946.

The first chemical analog of folic acid, "*X*-methylfolic acid," was a potent leukopenic agent whose activity was reversed by folic acid itself (Jukes *et al.*, 1950). Concomitantly, the groups in Pearl River, New York, and Bound Brook, New Jersey, were vigorously pursuing this "nutritional" problem (Franklin *et al.*, 1947a,b; Seeger *et al.*, 1947), and in 1948 4-aminofolic acid, aminopterin, was found to produce temporary remissions in children with leukemia (Farber *et al.*, 1948). Within the year amethopterin (methotrexate), the 10-methyl derivative of aminopterin, had been synthesized (Cosulich and Smith, 1948); it was found to be a noncompetitive inhibitor of folate, whereas its toxicity and biological activity were found to be competitively reversed by reduced folates such as leucovorin and tetrahydrofolate (Burchenal *et al.*, 1949b). Aminopterin was found to inhibit the growth of Rous sarcoma; however, the required dose was lethal to chickens (Jukes *et al.*, 1950). Fortunately, the effective antileukemic dose in children was not lethal, as was demonstrated by Farber *et al.* (1948).

This brief introduction to antifolate therapy shows so clearly that animal tumor experimentation provided little background for or impetus to the use of antifolates in human cancer therapy. The massive amount of information now available on antifolates can be considered confirmatory and enlightening not only to the field of cancer chemotherapy but to essentially all areas of modern biomedical research.

As just mentioned, the first folate analog was *X*-methylfolic acid (Jukes *et al.*, 1950), the synthesis of which was followed in rapid succession by that of numerous derivatives of folic acid, some of which were aminated and/or methylated. Others were derivatives with amino acid deletions and substitutions as well as being aminated and/or methylated. The Sloan–Kettering Institute, in collaboration with the chemists, biochemists, and nutritionists at the Lederle Laboratories of the American Cyanamid Company, tested and evaluated these compounds in many biological systems and rapidly came to the conclusion that methotrexate (amethopterin) was the most promising agent as a potentially effective anticancer drug. In general, their conclusion was correct; however, the basis for the conclusion was not understood. During the 15 years in which the National Cancer Institute sponsored major programs on antifolates (1955–1970) the same conclusion was reached (Venditti *et al.*, 1960; Mead *et al.*, 1968).

Experimental cancer chemotherapy was begun in earnest, and in February 1949 the New York Academy of Sciences hosted a symposium entitled "Antimetabolites" (Miner, 1950). This meeting took place less than 3 years after the academy had sponsored the "Folic Acid Symposium" (Miner, 1946), at which time the structure of folic acid and a variety of factors were elucidated, defined, and identified. Stock (1950) presented the results of the Sloan–Kettering Institute's Division of Experimental Chemotherapy on the antitumor activity of aminopterin and methotrexate. Both analogs were shown to have antitumor activity at doses that were somewhat toxic to the host animals. The spectrum of activity was the same; however, the effective doses were higher for methotrexate. Philips and colleagues (Philips and Thiersch, 1949; Philips *et al.*, 1950) reported that both analogs produced the identical toxic manifestation (folic acid deficiency) in mice, rats, and dogs, the LD_{50} for methotrexate being 5- to 20-fold greater than that of aminopterin.

Burchenal *et al.* (1949a) described the use of methotrexate in the treatment of childhood leukemia, having obtained remissions similar to those described by Farber *et al.* (1948) for aminopterin. Simultaneously, Burchenal *et al.* (1949b) and Goldin *et al.* (1949) noted that the antileukemic and antitumor effects of methotrexate and aminopterin could be reversed by folic acid when folic acid was administered several hours before the analog.

During the next 2 years (1950–1952) acquired resistance of mouse leukemias to methotrexate was described by Burchenal *et al.* (1950b) and Law and Boyle (1950); the blocking effect of leucovorin (citrovorum factor) on methotrexate antileukemic activity was noted (Burchenal *et al.*, 1950a); and the rescue effect of leucovorin was described (Goldin *et al.*, 1953, 1954, 1955). The first highly resistant microbial mutant was selected (Burchenal *et al.*, 1951a), and the well-known microbiological assay for methotrexate was presented and used to evaluate the pharmacokinetics of methotrexate in man (Burchenal *et al.*, 1951b). Those were exciting times, times when the basis for effective cancer chemotherapy was being formed and every clinical response was a stimulus for a new

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