

**NOVEL APPROACHES TO
SELECTIVE TREATMENTS
OF HUMAN SOLID TUMORS**

Laboratory and Clinical Correlation

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

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Laboratory and Clinical Correlation

Edited by

Youcef M. Rustum

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PREFACE

The therapeutic efficacy of FUra has been attributed to its incorporation into cellular RNA and, to its inhibition of thymidylate synthase, leading to potent inhibition of DNA synthesis and DNA damage. Studies of cell lines *in vitro* and model systems *in vivo* have demonstrated that although mechanisms of sensitivity and resistance to FUra are multifactorial, in the presence of citrovorum factor (LV, CF, 5-formyltetrahydrofolate) the site of action of FUra becomes predominantly the pronounced and prolonged inhibition of thymidylate synthase. This action is the result of stabilization of the covalent ternary complex between FdUMP, an active metabolite of FUra, 5,10-methylenetetrahydrofolates, and thymidylate synthase. This effect of LV is thus an example of the concept of metabolic modulation.

CF is commercially available as a racemic mixture of diastereoisomers (6R and 6S). The 6R isomer is considered to be biologically inactive; the 6S isomer is the biologically active form that is metabolized intracellularly to form the various folate cofactor pools including 5,10-methylenetetrahydrofolates. Although the extent of metabolism of folates in normal and tumor tissues has not been clearly delineated, it has been determined that the formation of folypolyglutamates is primarily a function of schedule of CF administration, while the retention of significant concentrations of reduced folate is a function of the dose and also the schedule of LV. Thus, it appears that for optimal modulation of FUra activity several factors must be considered simultaneously. These include the dose and schedule of administration of CF, the initial intracellular concentrations of folypolyglutamate forms, the level of thymidylate synthase, and the degree and duration of inhibition of thymidylate synthase. It has also become apparent that the schedule of administration of FUra could play an important factor in determining the therapeutic selectivity of the modulation. The latter is also influenced by the absolute and relative intracellular concentrations of FdUMP and the competing metabolite, dUMP.

In addition to CF, several other modulators of FUra were considered, including N-(phosphonacetyl)-L-aspartate (PALA), α -interferon (IFN) and combination of CF/PALA/and/or INF. Although the precise mechanisms of IFN in the modulation of FUra are not clearly delineated, several possibilities were discussed, including effects on thymidine transport, alteration of the pharmacokinetic parameters of FUra, increase FUra incorporation into RNA and aberration of the observed *in vitro* increase in the level of thymidylate synthase following treatment with FUra. PALA, a potent inhibitor of pyrimidine biosynthesis via inhibition of aspartate transcarbamylase, potentiates the therapeutic selectivity of FUra by increasing its incorporation into cellular RNA, resulting in decreased level of thymidine kinase. As a consequence of these effects, utilization of salvage thymidine could be avoided, thus reducing the possibility of reversing the drug effect at the level of thymidylate synthase.

During this symposium, several drug combinations with FUra/modulator inhibitions, include cis-platinum, 5-fluoro-2'-deoxyuridine (FdUrd) were also discussed.

Furthermore, the role of continuous i.v. infusion of FUra and the role of chronobiology of FUra were also discussed.

Because of the results, FUra/CF modulation demonstrated that thymidylate synthase is an important target of antimetabolic action. As a result, several new, potent and specific thymidylate synthase inhibitors were also discussed. Some of these agents are at the preclinical development, while others have already entered Phase I and II clinical trials including ICI-D1694.

The major diseases of focus were advanced and adjuvant colorectal cancer, head and neck cancer and breast cancers.

This symposium addresses:

- What have we learned and where to go in further utilization of the concept of metabolic modulation?
- What is the therapeutic impact of altered modes of drug administration?
- Drug development: What are potential sites of intervention?

On the first day of this symposium, entitled "Novel Approaches to Selective Treatments of Human Tumors: Laboratory and Clinical Correlation" studies related to the mechanisms schedule association of FUra and FdUrd were discussed. It became apparent that the mechanisms of action of these agents is schedule dependent with FUra incorporation into RNA as the dominator of FUra action, when the drug was administered by i.v. push and thymidylate synthase and also when FUra was administered by continuous FU infusion. In contrast, thymidylate synthase inhibition appears to be the dominant site of action of FdUrd when administered by i.v. push and FUra incorporation into RNA appears to be the dominant site of action of FdUrd when administered by continuous i.v. infusion. Confirmation of the preclinical data could have significant impact on the future development of clinical protocols with these agents when administered alone and/or in combination with modulators. In addition, during the first day of the symposium, clinical update of FUra modulation by various modulators in advanced and adjuvant colorectal cancer were discussed.

On the second day of the symposium, an update of the present status of FUra modulation in adult carcinoma, breast and head and neck carcinomas as well as the initial clinical experience with a new antifolate, ICI-D1694 were discussed. This new antifolate as well as others, including LY231514, AG331, appears to be very promising.

On the third day of this symposium, advances in the molecular biology of cancer and the discovery of new sites of intervention for drug development were discussed. This new and exciting area of research, although at its initial stages of clinical application, holds considerable promise for the future.

The encouraging clinical results based on strong rationales derived from *in vitro* and *in vivo* laboratory studies, reinforces the need for further laboratory investigations aimed at optimization of conditions and parameters responsible for selective modulation of FUra. It is clearly evident from the results of clinical trials conducted to date that by delineation of mechanisms associated with therapeutic selectivity of fluoropyrimidine and other thymidylate synthase inhibitors clinical protocols can be designed with the potential for therapeutic efficacy that can produce greater response rate of survivors of patients with advanced solid tumor malignancy.

On behalf of the organizing committee, I would like to take this opportunity to thank the speakers, discussants and attendees for their valuable contributions to this symposium. The success of this symposium should be credited to the tireless and unselfish efforts of Ms. Gayle Bersani and Ms. Geri Wagner to who I am greatly indebted. We would like also to thank Ms. Cheryl Melancon and Ms. Mae Brown for their help in typing manuscripts, transcribing the discussions, and preparing correspondence.

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This symposium was held to honor David Machover, M.D. for his outstanding contributions to the clinical development of 5-fluorouracil/leucovorin modulation. Dr. Machover and his colleagues of Villijuf were the first to publish the positive results of 5-fluorouracil/leucovorin in patients with advanced colorectal cancer.

The manuscripts included in these proceedings do not represent contributions from all the symposium speakers.

Y.R. Rustum

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