

PREFACE

Knowledge gained concerning mechanisms of action of 5-fluorouracil (5-FU) alone, in combination with leucovorin (LV) in *in vitro* and *in vivo* preclinical model systems, provided the basis for clinical evaluation and validation of the therapeutic efficacy and selectivity of this modulation in the early 1980s.

For more than two decades, the therapeutic options for patients with advanced colorectal cancer have been 5-fluorouracil/leucovorin modulation (5-FU/LV) based therapy. Although significant improvement in overall response rate was achieved, there has been no significant benefit as far as overall survival. With this treatment modality, diarrhea, mucositis, and neutropenia are the dose-limiting toxicities. In contrast to bolus 5-FU/LV, protracted continuous infusion of 5-FU yielded similar overall response rates with hand and foot syndrome as the dose-limiting toxicity.

In attempts to improve further on the therapeutic selectivity and efficacy of 5-FU/LV modulation, new and more specific thymidylate synthase (TS) inhibitors such as Tomudex (ZD-1694) are under extensive preclinical and clinical evaluation. However, the response rate in colorectal cancer and the toxicity profile from this drug were similar to those observed with 5-FU/LV therapy.

In clinical and preclinical model systems, 5-FU is eliminated rapidly from the plasma with a $t_{1/2\alpha}$ of less than 10 min, and more than 85% of the injected dose of 5-FU is inactivated by dihydropyrimidine dehydrogenase (DPD) in normal and tumor tissues. The remaining 15% of 5-FU is activated via the anabolic pathways with a major fraction incorporated into cellular RNA. Preclinical results indicate that GI toxicity was associated with increased drug incorporation into cellular RNA. This suggests that the therapeutic selectivity of 5-FU may be improved by selective inhibition of PRPP transferase (PRPPT) in normal tissue, the enzyme responsible for phosphorylation of 5-FU into 5-fluorouracil-monophosphate (FUMP).

Several new treatment modalities are under evaluation: (1) the combination of 5-FU or its prodrug with an inhibitor of DPD (e.g., uracil and eniluracil) to prevent 5-FU degradation; (2) the use of PRPP inhibitor to reduce 5-FU incorporation into RNA of normal tissue (e.g., potassium oxonate); and (3) capitalizing on the differential expression of enzymes responsible for the activation of 5-FU prodrug, in normal vs tumor tissues (e.g., capecitabine).

S-1 is a new oral pyrimidine fluoride-based anticancer agent in which Ftorafur (FT) is combined with two classes of modulators, 5-chlorodihydropyrimidine (CDHP) and potassium oxonate, at a molar ratio of 1.0/0.4/1.0 for FT/CDHP/Oxo, respectively. FT is inactive until it is metabolized to 5-FU by thymidine/uridine phosphorylase. CDHP is a potent inhibitor of DPD, the enzyme responsible for degradation of 5-FU into therapeutically inactive but toxic 5-fluorodihydrouracil; CDHP is about 180 times more effective than uracil in inhibition of DPD *in vitro*. Oxo is a potent inhibitor of PRPPT. S-1 is in phase I and II clinical trials in patients with advanced colorectal cancer in Europe, Japan, and in the United States.

Capecitabine is an oral, inactive 5-FU prodrug that requires three-step activation to 5-FU with the final step of activation to 5-FU by thymidine/uridine phosphorylase.

Capecitabine has been approved by US FDA in patients with breast carcinoma and advanced colorectal cancer. In contrast, UFT is activated by thymidine/uridine phosphorylase to 5-FU with uracil as a DPD inhibitor.

Improving therapeutic selectivity is a major goal of anticancer drug development. The success of 5-FU/LV therapy in patients with advanced colorectal cancer demonstrated the important role of thymidylate synthase (TS) as a predictive marker for response to 5-FU-based therapy. The therapeutic roles of the other markers associated with metabolism of 5-FU and its prodrugs are under evaluation in preclinical and clinical settings.

Fluoropyrimidines in Cancer Therapy updates and reviews the mechanisms of action and therapeutic selectivity and efficacy of 5-FU, with and without leucovorin and its prodrugs in colorectal cancer therapy. The potential advantages and disadvantages of these agents and the role of predictive markers are reviewed here. Drawing on the knowledge gained to date with these agents when used individually, they are now being evaluated in combination with other drugs (e.g., irinotecan, oxaliplatin, and EGF inhibitors).

Youcef M. Rustum



<http://www.springer.com/978-0-89603-956-8>

Fluoropyrimidines in Cancer Therapy

Rustum, Y.M. (Ed.)

2003, XII, 326 p., Hardcover

ISBN: 978-0-89603-956-8

A product of Humana Press