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New anti-cancer agent S-1: metabolism based drug combination

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S-1 is a novel oral form of a tegafur (FT, a prodrug of 5-fluorouracil)-based antitumor agent combination. It combines two compounds, 5-chroro-2,4-dihydroxy-pyridine (CDHP) which inhibits DPD(dihydropyrimidine dehydrogenase, rate limiting enzyme of 5-FU catabolism) and mono-potassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate(Oxo) which reduces gastrointestinal toxicity by inhibiting ORPT(orotate phosphoribosyl-transferase, it phosphorylates 5-FU) in the gastrointestinal tract.

We have investigated the pharmacokinetics of each S-1 component and 5-FU in rats and dogs to evaluate the control of 5-FU metabolism and Oxo targeting.

The AUC and C_{max} values of 5-FU, the active metabolite of FT, increased markedly in dogs, 40 times in AUC and 50 times in C_{max}, after administration of the combined preparation than after administration of FT alone. After oral administration of S-1 to tumor (Yoshida sarcoma) bearing rats, the concentrations of FT, 5-FU, CDHP and Oxo in plasma, tumor and small intestine were determined. The concentration of 5-FU in the tumor, which is the target tissue for anti-tumor action, was highest among the tissues, and showed a long duration. The concentration of Oxo, which is added to reduce the toxicity in the digestive tract was high in the small intestine. On the other hand, the concentration of Oxo in the tumor was low, and was not considered to reduce the anti-tumor effect of 5-FU.

Pharmacokinetically the marked species difference in AUC and C_{max} values of 5-FU corrected by the dose in each body surface area was not observed in dogs and rats.

This research paper was presented during the 2nd Conference on Retrometabolism based Drug Design and Targeting, May 11–14, 1999, Amelia Island, Florida, USA

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Retrometabolic approaches in phytobiochemistry

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Our aim was to examine to what extent the principles of the retrometabolism-based drug and chemical design [1–3] may be applied or extended to the phytophysiological processes. As a basis of this hypothesis is the recognition that in living beings the fundamental biological laws and those of them that describe the enzyme systems, are the same. It seems that the possibilities of the soft drug approach are particularly promising. We have first expected immediately accessible results from the study of phytohormones, namely auxins.

The research of phytohormones represents the central field of the up-to-date phytophysiological investigations, where in the last decades two fundamental statements were born [4–10]:

1) the hormones of plants form a coherent functional system,

2) the phytohormones act on both genetical and metabolic levels.

Auxins are implicated in a wide variety of developmental processes in plants, including elongation growth, photo- and gravitropism, apical dominance, lateral root initiation, the differentiation of vascular tissues, embryogenesis and fruit ripening. Auxin has an autoregulating activity, i.e. it induces the formation of decomposing enzymes (e.g. auxin-oxydase) increasingly with the age of the plant. By this regulation the equilibrium between the growth and metabolism is ensured, too.

The action mechanism of auxin is disputed. Experimentally it is known that their growth-stimulating activity as a function of the concentration passes over a maximum (optimum). For its explanation frequently the "two points theory" is accepted. The occurrence of the phenomenon (the appearance of the maximum) could be explained by the inhibitory effect of the gradually multiplied free radicals having appeared due the decompositions caused by auxin-oxydase, too. These two cause-effect relations are not compulsorily independent on each other.

This image is more complicated by a fact known from literature [11]: indole-acetic acid (IAA), above the optimal concentration, induces formation of ethylene, being itself a growth factor, mainly an inhibitor. Possibly, auxin releasing ethylene influences the m-RNA synthesis, thus of the enzymes, too.

Our hypothesis was that replacing the $-CH_2-CH_2-$ structural unit in the "hard" indole-butyric acid (IBA) molecule with the isosteric/isoelectronic $-C(=O)-O-$ and $-O-C(=O)-$ group (ester or reversed ester functions), according to the usual synthesis of "soft" analogues [2], the amount of the phytotoxic metabolic products will decrease. If the oxidative metabolic products inhibit the growth-stimulating effect, one should wait for a modification of the growth-concentration curve form in the case of soft analogues, and the character of these modifications will supply information to the more detailed understanding of the action mechanism.

Our preliminary research results are represented concisely by the curves in Figs. 1 and 2. We followed the stimulating effect by measuring the growth in length of the etiolated oat coleoptiles, in different hormone concentrations, in