

Consequences of Amino Acid Deprivation in Combination Chemotherapy

In describing the multiple activities of histidinol as a single agent and in combination, Stolfi and Martin (1) stated "The effect of histidinol and histidinol/drug combinations appear to be different in different tumors. Histidinol alone can have no measurable effect on tumor growth *in vivo*, or it can protect the host while allowing an unimpeded attack on the tumor by a chemotherapeutic drug and in some instances even accentuating the chemotherapeutic effect, while in another system it can protect the host, but reverse the cytotoxic action of the chemotherapeutic drug in the tumor. Such a pattern of results is not surprising in light of the known biochemical heterogeneity of malignant tumors. However, this pattern of response emphasizes a technically difficult problem that must be confronted, if we are going to make useful progress in the development of modulatory techniques to improve the therapeutic efficacy of currently available chemotherapeutic agents".

In this correspondence, some specific reactions comprising the biochemical heterogeneity of malignant tumors are described together with their impact on combination chemotherapy.

Since histidinol is recognized as an inhibitor of histidine activation in the formation of histidyl-transfer RNA (tRNA) for protein synthesis (2,3), the above anomalies could be inherent through this mechanism. A similar result of amino acid deprivation is obtained through the administration of interferon, especially interferon gamma. In many cell types, this agent causes the induction of indole oxygenase, which, by degrading tryptophan, brings on a tryptophan deficiency. The implications of this deficiency on cell metabolism and chemotherapeutic potential have been reviewed (4,5), and it is perhaps through this mechanism that

interferon inhibition of induction of thymidine synthase is the basis for combination therapy with interferon gamma plus fluorouracil (6). Thus, both histidinol and interferon gamma can act as modulators of cancer therapy by inhibition of proliferation through an amino acid insufficiency and the resulting accumulations of uncharged tRNA.

Fluorouracil can enter the metabolic pool by either of two routes (7). One route uses the enzyme orotate phosphoribosyltransferase (OPRTase) to catalyze the condensation of the fluoropyrimidine with phosphoribosylpyrophosphate (PRPP). This route is prevalent in murine adenocarcinomas (8). An alternative route that does not require PRPP involves the sequential action of uridine phosphorylase and uridine kinase (7). The synthesis of PRPP from glucose is markedly reduced by amino acid deprivation (9). Since such deprivation would prevent fluorouracil from entering the metabolic pool, as found by Sawyer et al. (10), such conditions would block the efficacy of the fluoropyrimidine in both toxicity to the host and therapeutic activity (11). Edelstein and Heilbrun (12) were able to circumvent this limitation by infusing histidinol after the administration of fluorouracil, thus permitting its reaction with PRPP to occur before the block in its synthesis began. Also, by using an infusion instead of injections, they obviated the limitation of a short circulatory life, as reported by Zaharko et al. (13). Such pharmacokinetic limitations as well as metabolic turnover may be the reason a decrease in PRPP was not seen during histidinol treatment (10).

The mechanism by which an amino acid deficiency decreases the cellular PRPP content has been shown to be due to the inhibition of phosphofructokinase by uncharged tRNA (14,15). This mechanism limits the availability of fructose-1,6-diphosphate, which on further metabolism yields glyceraldehyde-3-phosphate, a critical component in the synthesis of PRPP by tumor cells (16). This mechanism also serves to explain the observation that histidinol administration interferes with multidrug resistance (17). Since an increased glycolytic energy source is required for expression of resistance (18),

interference with glycolysis through the mechanism proposed above would reduce the required energy available for expulsion of the drug.

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