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 accumulation 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.

References

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An Open Letter to Cancer Center Directors

Through your leadership and guidance you have the ability to exert a great influence on the lives of your patients, their friends, and their families. It is for this reason that I wish to share the following experience with you.

My niece, who is in her mid-30s and has a small child, was diagnosed (in a small town) with breast cancer that had metastasized to the bone. Her doctor referred her to an oncologist who, after examining her, suggested that there was little hope for long-term survival. Her husband then took her to a major comprehensive cancer center for another opinion. There, the oncologist stated that chemotherapy might keep her alive for 2-5 years, but that he was uncertain if it was worth going through the agony. Her husband had watched his mother die a painful death from breast cancer some 20 years before, so he realized what was in store for his wife.

They were shaken by the initial diagnosis but knew that the first physician was not a trained cancer specialist. When the first oncologist predicted doom and gloom, they were again upset but they realized that this was only one opinion. However, after hearing a similar assessment from another oncologist, this time at a major cancer center, they felt that they had exhausted all options and that all hope was lost.

When I learned what had transpired, I suggested that they call an oncologist some 2000 miles away who is reputed to be a top breast cancer physician. He suggested that she come to see him the very next day. After consultation and tests, he decided to treat her immediately. She received her first course of chemotherapy within 24 hours of the phone call. He told her that with the aggressive treatment regimen he planned for her, there was an 80% chance that her disease would go into remission. Obviously, I cannot speculate as to whether the therapy will be successful, but the ray of hope extended to her by this doctor gave her the will to fight for her health and her life. I am convinced that win, lose, or draw her quality of life was positively impacted.¹

Doctors need to be conscious of and concerned with the way they talk to their patients. Doctors working at cancer centers should be particularly aware of how important it is that they speak accurately, compassionately, and always with concern for the patient and his or her quality of life. Very often patients are looking to these doctors as their last and best hope. No matter how busy, an oncologist needs to take time to search for the best answer for each and every patient. Ask your physicians to treat their patients as they would like themselves to be treated and to pursue even seemingly remote possibilities. Oncologists should be trained to admit that there will be occasions when a peer may offer a better prognosis. And finally, they should be reminded that their demeanor, words, and decisions affect many people, not just their patients.

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Notes

¹Author’s note: It is now nearly 3 months [at the time this correspondence went to press in early December] after the original diagnosis and commencement of treatment. Three courses of the supposedly ineffective chemotherapy have shrunk the original 7-cm × 4-cm × 3-cm tumor to less than 1 cm × 1 cm × 1 cm. But as important as the results are the fact that they were accomplished with relatively no adverse side effects other than feeling tired. The patient has continued to lead a full, active life.

Editors note: Richard Bloch served as a member of the National Cancer Advisory Board from 1982 to 1988.

Menstrual Cycle Timing of Breast Cancer Resection: Prospective Study Is Overdue

In 1987, it was determined that the timing of breast cancer resection within the mammalian fertility cycle affected the metastatic potential of mouse breast cancer (1) and that the most relevant cellular defenses against metastasis, natural-killer cell activity (2) and endogenous interleukin 2 production, covaried precisely with surgical curability. Armed with these data, I attempted to convince the leaders of each major cooperative cancer study group that it should be determined whether such a relationship exists in young women. I argued that very simple changes in the “on study forms” for premenopausal patients considered for an adjuvant breast cancer trial would prospectively address this question, that there was no apparent risk to obtaining information about the timing of the last menstrual period at the time of resection, and that the potential benefit of optimally timed surgery was worth pursuing. These efforts were redoubled in 1988 when it was discovered that the timing of breast cancer resection within the menstrual cycle was relevant.

Operations performed during the putative early luteal phase of the cycle were associated with improvement in the 10-year disease-free and overall survival (3). Seven additional series that included some 2000 young women have subsequently confirmed these observations (4). Still, several negative retrospective studies raise the possibility that this relationship is not so simple. While a few institutions and individuals have modified their surgical practice to accommodate these data, the vast majority of practicing surgeons remain unconvinced (5,6). I remain unable to easily persuade those in the positions to do such studies that this is a high priority.