Cancer Chemotherapy: An Unexpected Drug Interaction

Many commonly used regimens for combination chemotherapy of tumors may have to be revised if preliminary results from two San Francisco investigators are confirmed. Daniel V. Santi and David W. Martin of the University of California find that one of the most frequently used antitumor agents, methotrexate, interferes with the activity of another antitumor drug, 5-fluorodeoxyuridine (FldUrd) given at the same time, in tests on tumor cells grown in culture. The evidence suggests that it should also interfere with the activity of the more frequently used antitumor drug 5-fluorouracil, which is believed to have the same mechanism of action as FldUrd. Methotrexate and 5-fluorouracil have been used together in the therapy of many forms of cancer, including tumors of the breast, head, neck, liver, colon, and rectum. Santi and Martin's results have not been published yet, but they have been presented to the National Cancer Institute (NCI) and have spurred that agency to reinvestigate the effects of the two drugs in animals.

Maximum Efficacy, Minimum Toxicity

Combination chemotherapy has made major improvements in the treatment of cancer during the last decade. It is based on the use of several drugs, occasionally as many as six, whose mechanisms of action and side effects are different. When the drugs are combined under the appropriate schedules of administration, the therapeutic advantage is maximum and the toxicity is minimum. Most such treatment regimens have been developed empirically from what is often only a rudimentary understanding of the mechanisms of action of the drugs. The system studied by Santi and Martin is one of the few instances in which a detailed knowledge of the biochemistry is available both to predict situations that should be avoided and to indicate ways in which the chemotherapy can be improved.

Both FldUrd and 5-fluorouracil are metabolized to a third compound, FldUrd monophosphate, that is the active form of the drug. The monophosphate inhibits the activity of thymidylate synthetase, an enzyme that takes part in the biosynthesis of DNA; the drug thus inhibits the synthesis of DNA and impairs the replication of tumor cells. Methotrexate inhibits an enzyme that is important in the conversion of folic acid to 5,10-methylenetetrahydrofolic acid, which is a cofactor in the reaction of thymidylate synthetase. In effect, then, methotrexate also inhibits thymidylate synthetase, and many scientists have assumed that its activity would be complementary to that of FldUrd or 5-fluorouracil.

Santi's key finding is that FldUrd monophosphate can bind strongly to thymidylate synthetase, and thus inhibit it irreversibly, only in the presence of 5,10-methylenetetrahydrofolic acid. In the absence of the cofactor, its binding constant to the enzyme is weaker by a factor of 10^8, and the inhibition is proportionately weaker. This effect has also been demonstrated by Charles Heidelberger of the University of Southern California, who originally discovered the antitumor properties of 5-fluorouracil. Santi therefore reasoned that methotrexate, which inhibits its biosynthesis of the cofactor, could interfere with the activity of 5-fluorouracil and FldUrd.

Buddy Ullman and Melinda Lee of Martin's laboratory tested this theory in two different types of cultured mouse tumor cells and found that it was correct. They observed that methotrexate decreases the efficacy of FldUrd against both types of cells. They also found that the efficacy of FldUrd was substantially decreased when the tumor cells were deprived of folic acid, which suggests that the postulated mechanism for reduced efficacy of the combination is the correct one.

Martin and Santi then contacted NCI and obtained the limited amount of available data in which tumor-bearing mice were treated with the two drugs. Both they and NCI interpret these data as showing that there are no additive effects when the two are used together. The data are not definitive, however, and NCI plans to rerun the experiments as soon as personnel becomes available. The agency will also study the effects of 5-fluorouracil on mice that have been deprived of folic acid if appropriate techniques can be developed.

Part of the indeterminancy of the animal tests may arise from the administration schedule of the drugs, Martin says. The activities of the drugs can be complementary if they are given in the proper sequence. If methotrexate is given before FldUrd, or at the same time, its irreversible effects on synthesis of the cofactor inhibit the action of FldUrd. But if it is not given until after the effects of FldUrd have reached their peak, then the effects of the two drugs should be additive.

Because 5,10-methylenetetrahydrofolic acid is so important to the activity of FldUrd, they looked at closely related compounds to see if they produced the same effect. Several synthetic analogs can replace the cofactor, but the best effect is achieved with the naturally occurring vitamin 5-formyltetrahydrofolic acid, also known as leucovorin or folinic acid. (The cofactor itself cannot be administered exogenously because it will not make it to the enzyme site intact.) In the tissue culture experiments, Martin finds that folinic acid will completely reverse the antagonism between the two drugs and allow maximal efficacy of FldUrd. And in cells deprived of folic acid, folinic acid increases the efficacy of FldUrd by a factor of 5.

This effect could be very important in advanced cancer patients, many of whom are known to suffer from a deficiency of folic acid as a result of cachexia. Unless these patients receive a replacement for the folic acid, then neither 5-fluorouracil nor FldUrd will be as effective as they could be. Since folinic acid is a vitamin, furthermore, no approval from the Food and Drug Administration will be required for its clinical use. The NCI will test the effects of folinic acid given in conjunction with 5-fluorouracil in mice, and Martin and Santi hope to get other investigators interested in studying its effects in animals and in humans.

Question Marks

There are several important question marks associated with Santi and Martin's research. Although Heidelberger says that the mechanisms of 5-fluorouracil and FldUrd are identical, it has not yet been shown that methotrexate inhibits the activity of 5-fluorouracil. The two investigators are performing those experiments now. Furthermore, their results must be extrapolated from findings in tissue culture systems to results in animals, and then on to humans. They have used tumor-cell systems that are normally used by NCI for screening of chemotherapeutic agents, and the track record for extrapolation to humans of results obtained in these cells is good, but the studies in animals and humans must be performed before their results can be shown to be important for therapy. But if all of these reservations are overcome, according to Saul A. Schepartz of the NCI, then clinicians may have to revise their treatment regimens accordingly.

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