Understanding Trimetrexate Toxicity

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Cellular metabolism of folic acid in general and dihydrofolate reductase (DHFR) in particular has proven to be an intriguing target for experimental chemotherapy agents in the treatment of both cancer and infectious disease. The attractiveness of this approach stems from the central role of DHFR in the maintenance of cellular concentrations of reduced folic acid cofactors, which are essential for the synthesis of both purine and pyrimidine nucleotides. The success of methotrexate as a clinical antineoplastic drug over several decades has added to the impetus for discovery of new antifolates. The development of trimetrexate (TMTX), a nonclassical 2,4-diaminoquinazoline antifolate, represents one of the more recent attempts to exploit this important mechanism of action clinically.

Clinical studies with TMTX were approached with great enthusiasm for several reasons (1-3). This compound is a potent inhibitor of both mammalian and protozoal DHFR; it had demonstrated a high level of antitumor activity against a broad range of experimental neoplasms and, perhaps most importantly, had shown the capability of overcoming two of the potential mechanisms for clinical methotrexate resistance. The ability to circumvent cellular resistance resulting from decreased drug transport or low-level elevations of cellular DHFR was viewed as an advantage of potentially great significance.

Phase I trials were carried out on a number of schedules, and several consistent features emerged (4-9). The toxic effects were very reminiscent of those of other antifolates, with mucositis and myelosuppression predominating. There was marked variability among patients in tolerance to the drug. Sporadic instances of serious toxic effects occurred at or near the starting dose for several schedules, but the reasons for these observations were not evident in any single trial. Evidence of antitumor activity was seen in a number of diseases even in these early studies. The majority of phase II trials were initiated with a schedule of daily doses for 5 days; this approach was supported by the striking schedule dependency observed in P388 leukemia in mice receiving multiple daily doses (1).

The unacceptably high incidence of severe and life-threatening toxic effects observed in the initial phases of these trials prompted Eisenhauer and her colleagues to review the characteristics of patients entered in their studies and Grem et al. to review the experience in National Cancer Institute-sponsored phase I trials for characteristics that might herald these untoward effects. The important information these analyses yielded is found in these two reports in this issue of the journal. The authors have concurrently identified hypoalbuminemia or hypoproteinemia as significant predictors of excessive TMTX toxicity. The Canadian group (Eisenhauer et al.) also demonstrated that the presence of liver metastases confers an increased risk for toxic effects, and they suggested that this risk is additive with that of low serum protein levels. Grem et al., in analyzing a distinctly different patient population, demonstrated that patients with leukemia have an increased sensitivity to the toxicity of TMTX and that the dose and schedule of administration were important determinants of toxic effects when the larger variability of both parameters intrinsic to phase I trials became a factor.

The immediate and perhaps most important impact of these observations has preceded their publication; in phase II trials of TMTX, patients identified as being at high risk for toxic effects on the basis of serum protein concentrations have received attenuated doses. While the validity of these characteristics as predictors of toxic effects has not been evaluated prospectively, the strong impression remains that patient safety has been maximized.

Importantly, these insights have been gained by examining the combined data from a number of studies conducted at different institutions and were possible only because the raw clinical data were available to the authors of these two studies as representatives of the sponsoring agencies. With all of the potential shortcomings of this type of analysis, the likelihood is that this information would not have become available to clinical investigators without the existence of these combined clinical data bases. In recent years, the process by which new antineoplastic drugs are evaluated has been strengthened in a number of important areas. Improved methods have been sought to screen compounds for promising antitumor activity; a more efficient toxicology protocol has been developed; the role of pharmacology in the design, conduct, and interpretation of studies has been emphasized; and more rigorous criteria for reporting the results of clinical trials of new agents have been increasingly adopted. The effective use of a large clinical data base for analyses such as these and the ability to use the information in ongoing clinical trials should be included among these modest but important improvements in this process.

The results of these two studies must, however, be considered preliminary, and the questions they raise should be addressed in future studies. Why, for example, does hypoalbuminemia predispose one to toxic effects from TMTX? Is it simply a matter of an alteration in TMTX protein binding?
that affects drug clearance? Alternatively, is the low albumin level an indirect reflection of an intrinsic defect in hepatic clearance of the drug, or does it reflect the compromised physiologic status of patients, a condition predisposing them to toxic effects in the absence of any pharmacologic perturbation? Although both studies identify serum protein status as an important predictor of toxic effects, why is there not a more consistent trend in toxic effects with changing albumin or protein concentration (Grem et al.)? Similarly, the relationship between the physiologic status of the liver and the tolerance of the patient to TMTX must be further investigated. In view of the complex relationship between protein binding and the kinetics of drugs in liver disease, these factors are inextricably linked (10,11). Although the liver is principally thought of as a major site for metabolic clearance of drugs, liver disease can have profound effects on tissue distribution and protein binding independent of the serum protein concentration. Consequently, the effect of hepatic dysfunction on drug disposition is neither predictable nor consistent. There is a need for carefully done pharmacologic studies with attempts to establish (a) relationships between the physiologic status of the patient and the drug's pharmacokinetic behavior and (b) pharmacodynamic correlations with the relevant clinical end points. In the absence of such studies, only speculation is possible about the mechanisms underlying these clinical observations. The results of the study of Fanucchi et al. (4) support the concept that albumin concentration affects drug disposition. The study shows that total-body clearance of TMTX is positively correlated with serum albumin and inversely correlated with thrombocytopenia. Further study of this important finding is warranted. Because the eligibility criteria for early clinical trials preclude entry of patients with more than modest liver dysfunction by usual clinical criteria, the influence of more seriously impaired liver function on toxic effects has not been addressed. Both Grem et al. and Eisenhauer et al. noted that a pharmacologic study of TMTX in patients with altered physiologic states of liver and kidney function or large ascites or pleural fluid accumulations has been planned, and we anxiously await its activation. It should be emphasized that information with this degree of detail is available for few, if any, of the drugs we use commonly in oncology practice. The amount of information expected to be provided by early clinical trials of new modalities is expanding rapidly, and appropriately so.

The logical recommendation for treatment of patients in high-risk groups is that they receive lower doses of TMTX in the first course of therapy. The multivariate analysis of Grem et al. using data from solid tumor patients identifies the schedule of administration as a significant predictor of toxic effects in addition to protein concentration and dose. This raises the possibility that schedules other than administration daily for 5 days, which appears to result in the most severe toxic effects, should receive broader evaluation. It has not been determined whether the schedule dependency observed in mice will be equally applicable to humans; in mice, extremely rapid disappearance of drug from plasma requires repeated doses for optimal therapeutic effect, but in man, the plasma half-life is 10–15 hours. The apparent toxicologic advantage of other schedules may provide the additional rationale to broaden this study.

References