This approach is the hypothesis that we are currently testing, with good preliminary results with respect to tolerance and feasibility of an intravenous complete glucose-free nutritional regimen plus hydrazine sulfate (7).

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REFERENCES


NOTE

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In his reply to my letter in a recent issue of the Journal (1) stressing the incompatibility of tranquilizers with monoamine oxidase (MAO) inhibitors in the National Cancer Institute (NCI)-sponsored studies of hydrazine sulfate, Dr. Wheeler states that there is considerable evidence that use of these medications (tranquilizers) was “inconsequential,” since “the addition of medications that could potentially interact with MAO inhibitors in some patients did not statistically increase toxicity.” This statement derives, at least in part, from NCI’s retrospective statistical analyses of the largest of its hydrazine sulfate studies, containing a series of nine survival analysis figures, as submitted by the Cancer and Leukemia Group B to the U.S. General Accounting Office (2). These retrospective analyses and their underlying statistics were submitted to senior consultant biostatistician R. D. Wilkins for an independent analysis. In an 18-page report (3), Wilkins found that, due to “nonreparable defects,” the NCI retrospective analyses, “as presented, cannot statistically substantiate any claim that use of adjunctive tranquilizers and/or barbiturates had no (deleterious) effect on hydrazine sulfate drug action or survival outcome.” These concerns of lack of statistical validity of the NCI retrospective analyses were echoed by additional statistical sources available to the General Accounting Office (4).

Again, there is simply no pharmacologic justification for the use of tranquilizers and/or other medications known to be incompatible with MAO inhibitors during the clinical testing of a powerful and irreversible MAO inhibitor such as hydrazine sulfate. Dr. Wheeler’s concerns for quality of life, although understandable and laudable, could easily have been answered by use of agents, such as metaclopramide with or without adjunctive corticosteroids, that are compatible with hydrazine sulfate, can safely be given with the drug, and are equally effective in relieving the nausea and associated side effects of cisplatin-based chemotherapy (5).

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REFERENCES


NOTE

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RESPONSE

I appreciate this opportunity to reply to Dr. Bozzetti’s (1) concerns about the use of hydrazine in cancer patients with respect to glucose metabolism. Although it is possible that hydrazine could be shown to be useful in a differ-
ent context from that used in the three previous randomized trials (2–4), there is no evidence as yet that this possibility is true. In the context that it was used, hydrazine showed no benefit. If the final results of Dr. Bozzetti’s current trial turn out to be as good as his preliminary results suggest, perhaps these results would encourage interest in further studies. Any treatment that truly benefits cancer patients is welcome. However, once a treatment has clearly been shown not to work, its lack of efficacy should be accepted and its continued use should not be proposed unless new clinical evidence becomes available. On the basis of what we now know, there is no justification for another randomized trial with the use of hydrazine when much more promising clinical ideas are competing for scarce research funds.

As to Dr. Gold’s letter, I cannot comment on his statistical assertions because I could not review his references from letters sent to the U.S. General Accounting Office (GAO) or the article from Penthouse magazine. However, the GAO report that resulted from his allegations entitled “Cancer drug research: contrary to allegation, NIH hydrazine sulfate studies were not flawed” (5) is available. Dr. Gold’s basic assertion has been that the studies were flawed because of the concurrent use of tranquilizers, barbiturates, and/or alcohol with hydrazine. The GAO report noted that there was controversy over whether his concerns about incompatibility had been scientifically validated in humans. The National Cancer Institute (NCI) and researchers from the Cancer and Leukemia Group B and the North Central Cancer Treatment Group (NCCTG) reviewed the same (mostly) preclinical reviewed by Dr. Gold and concluded the following: 1) that there was no objective evidence or published studies in humans that addressed interactions between hydrazine and the alleged incompatible medications to support Dr. Gold’s contentions; 2) that unpublished animal data did not support the hypothesis that short-term use of tranquilizing agents with hydrazine would increase toxicity or decrease benefit; and 3) that at most, Russian animal data suggested that large doses of alcohol or barbiturates might increase toxicity (neither of which was used at these doses in any of the randomized trials). Dr. Mikhail Gershano-vich, one of Russia’s leading cancer spe-

cialists and a principal author of the Russian hydrazine studies (6), was interviewed and stated that he had no evidence of incompatibility between hydrazine and tranquilizers. The GAO report concluded that “subsequent analyses of patients’ use of concurrent medications did not invalidate NCI conclusions that the drug [hydrazine] was ineffective.”

One further point from the GAO report has not yet been published in the medical literature. In the NCCTG lung cancer trial (3), ondansetron, which does not interact with monoamine oxidase inhibitors, became available in early 1991 and was used in 91 patients, replacing benzodiazepines. Retrospective subset analysis of those patients in the hydrazine arm who received either ondansetron or benzodiazepines showed no statistically significant differences in survival time or time to disease progression between the two groups. Thus, even patients who received hydrazine without any of the medications objected to by Dr. Gold still did not show any benefit. My previous conclusion remains valid; namely, that there is considerable evidence that the use of the medications that Dr. Gold objects to were inconsequential in limiting the efficacy or increasing the toxicity of hydrazine.

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REFERENCES


NOTE

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