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*Letter to the Editors*

# Phase I Clinical Trial with a Combination of Methotrexate and Mitomycin C

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Synergistic antitumor activity was recently reported in experimental tumor models with a combination of methotrexate (MTX) and mitomycin C (MMC) (3). A combination of these agents was deemed of interest for a variety of human neoplasms, in particular head and neck cancer (1,4). We embarked on a pilot study in solid tumors using MMC on day 1 and MTX on days 1 and 8. Both agents were given by rapid IV injection. Upon entry into the trial, all patients had normal WBC ($\geq$4,000/mm$^3$) and platelet counts ($\geq$100,000/mm$^3$), as well as normal serum creatinine and bilirubin levels. On day 8, the dosage of MTX was reduced by 50% if WBC counts were 2,000-2,999/mm$^3$ and/or if platelet counts were 50,000-99,000/mm$^3$. The drug was withheld with lower values and in the presence of stomatitis. Courses were repeated every 4 weeks, after apparently full recovery of all toxic effects.

Eight patients entered the trial and received a total of 20 courses. All but one patient had advanced head and neck tumors. The remaining patients had squamous cell cancer of unknown origin. All patients had prior radiotherapy, six had prior surgery and two had prior chemotherapy consisting of m-AMSA, carminomycin or bleomycin. None of the patients was eligible for chemotherapy programs of higher priority, mainly because clearly measurable lesions were lacking. Median age was 53 years (range: 43-71) and median performance status on the Karnofsky scale was 75 (range: 50-90).

The daily dose of MTX ranged from 33 to 50 mg/m$^2$ and that of MMC varied between 6 and 10 mg/m$^2$. Myelosuppression was the main toxic effect observed in this trial as assessed by weekly blood counts. At the highest doses that were investigated, the regimen consisted of MMC 10 mg/m$^2$ on day 1 and MTX 50 mg/m$^2$ on days 1 and 8. Five patients entered the trial at this dose level. During the first course of therapy, two had no myelosuppression, one had moderate leukopenia with 1,800 WBC/mm$^3$, and two had life threatening hematologic toxicity with nadir WBC of 0 and 100/mm$^3$ respectively and corresponding platelet counts of 600 and 700/mm$^3$. These two patients developed reversible infectious and hemorrhagic complications. They were relatively good-risk patients in terms of age and performance status and had received no prior chemotherapy. After complete recovery, both were retreated with 2/3 of the previous MMC and MTX dosages for 1 and 3 courses respectively. Myelosuppression was encountered only in the second patient with successive WBC nadirs of 11,800; 2,800; and 1,500/mm$^3$ and corresponding platelet nadirs of 228,000; 83,000; and 2,000/mm$^3$. During the last course, MTX had been withheld on day 8 because of a moderate leukopenia of 2,900 WBC/mm$^3$. Considering all toxic courses at all dose levels, the median time to nadir was 15 days and full recovery of WBC and platelets was generally achieved by day 22.

Non-hematological toxic effects consisted of gastrointestinal intolerance and stomatitis. Mild to moderate nausea and vomiting was seen in one-half of the courses. Three patients experienced moderate to severe stomatitis. Two of these received the combination at the highest dose level and also had life-threatening myelosuppression.

This trial was not designed to assess the response rate to our regimen. One patient had a subjective response whereas the disease progressed objectively in three patients.

To summarize, at the dose schedules that were explored, the combination of MMC and MTX appears to induce unpredictable hematologic toxicity. In addition, rapidly cumulative myelosuppression may also be encountered. Others have recently incorporated MMC and MTX in combination chemotherapy regimens (2,5), but insufficient information is available to compare their toxicity findings with ours. In any event, our observations make our combination unattractive for further investigations despite the small number of patients treated in the study.

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