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Letter to the Editor

Pilot Phase II Trial of Amphotericin B and CCNU in Renal and Colorectal Carcinomas

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MEDOFF, Valeriote and Dieckman [1] demonstrated that in AKR leukemia, Amphotericin B (AmB) enhanced the antitumor effect 180-fold for cyclophosphamide, 330-fold for adriamycin, 209-fold for nitrogen mustard, and over 1000-fold for CCNU. We therefore studied AmB combined with CCNU in renal cell carcinoma and colorectal carcinoma. Thirteen patients with colon carcinoma resistant to standard 5FU therapy and five patients with renal cell carcinoma resistant to progestins received adequate therapy. All patients received AmB 7.5 mg/m^2 day 1, and 30 mg/m^2 day 2. Following completion of the AmB on day 2, CCNU 120 mg/m^2 was administered orally. Therapy was repeated every 6–8 weeks. The CCNU doses were adjusted for myelosuppression. Ten patients with colorectal carcinoma were evaluable (two lost to follow up, one not measurable). Four were resistant to nitrosoureas. All five patients with renal cell carcinoma were evaluable.

None of the 10 patients with colorectal carcinoma and none of the five patients with renal cell carcinoma had a partial response (greater than 50% reduction in tumor area). In no patient did disease remain stable for greater than two courses of therapy. One patient with renal cell carcinoma and four patients with colorectal carcinoma died during the first courses of therapy.

The dose-limiting toxicity in this treatment program was myelosuppression. Moderate to severe thromocytopenia (<75,000/mm^3) was observed in 36% of patients, and severe granulocytopenia (<500/mm^3) was observed in 11%. Mild to moderate leukopenia (500–1500/mm^3) was observed in 36% of the patients. Twenty-seven per cent of patients showed a significant fall in their hemoglobin concentration greater than 3 g/dl. Thirty-six per cent of patients suffered mild or moderate nausea and vomiting. Over 50% of patients experienced chills and fever despite administration of diphenhydramine and acetaminophen prior to the AmB.

Considering the remarkable synergism which had previously been demonstrated between AmB and CCNU experimentally [1], we were disappointed to observe 10 consecutive failures in patients with colorectal carcinoma, and five consecutive failures in patients with renal cell carcinoma. At a 90% confidence interval, this excludes a response rate of greater than 21% in colorectal carcinoma, and excludes a response rate of greater than 37% in patients with renal cell carcinoma.

We conclude that in colorectal carcinoma and renal cell carcinoma, diseases which are both minimally responsive to nitrosoureas, there is no clinically observed synergistic interaction between AmB and CCNU when used in this schedule. The concept of potentiation of antitumor drugs by administration of membrane-active agents continues to be attractive. Future studies could test the administration of nitrosoureas with AmB in other diseases perhaps more similar to AKR leukemia (lymphoid malignancies or tumors with high growth fractions, such as small cell carcinoma of the lung). Furthermore, potentiation of nitrosoureas by membrane-active agents might require longer administration of AmB, or the use of other polyenes.

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