Cancer Chemother. Pharmacol. 1, 73–75 (1978)

Cancer Chemotherapy and Pharmacology

Short Review

Mitomycin C: Experience in the United States, with Emphasis on Gastric Cancer

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Mitomycin C is an antibiotic alkylating agent isolated from the fermentation of *Streptomyces caespitosus* in 1958. Clinical trials were initiated in Japan soon after the demonstration of antitumor activity against a broad spectrum of transplanted animal tumors [2]. Mitomycin C was reported to have a high degree of efficacy for human cancer, which prompted a cooperative multiinstitution evaluation of this agent in the United States. A preliminary summary of the results of the initial experience was reported in 1959 by Jones [11]. Of 120 patients treated, objective responses were observed in 21 (18.5%) including breast cancer, Hodgkin's disease, lymphocytic lymphoma, and chronic granulocytic leukemia. Treatment was discontinued in 87% of patients because of severe hematologic toxicity. It was concluded that mitomycin C had an extremely narrow therapeutic index, while demonstrating only limited efficacy. The result was a sharply reduced interest for mitomycin C as an anticancer agent in the United States.

Because of the variance in results from Japanese and American investigators, Frank and Osterberg in 1960 undertook an analysis of 14 clinical trials conducted in Japan [7]. A total of 351 individual case records were reviewed using the following criteria as evidence of an objective response: reduction in tumor size, decreased pleural or ascitic fluid, marked reduction in jaundice, or a significant improvement in peripheral blood or bone-marrow findings in patients with leukemia. The overall tumor response was found to be 37%. Responses were recorded in gastric cancer (35%), breast cancer (42%), and lung cancer (37%). In addition, higher levels of activity were recorded in a smaller number of patients with chronic myelogenous leukemia, reticulum cell sarcoma, and seminoma. It was found that both toxicity and antitumor effect were a function of the total dose administered. Hematologic toxicity was an accompaniment of tumor response in 68% of cases and was severe in cases that had received a cumulative dose of 40–50 mg.

In the same year, Ferguson and Humphrey introduced a dose schedule of 50 μg/kg for 6 consecutive days followed by alternate day treatment until toxicity [6]. This regimen was to remain a standard method of administration of mitomycin C in the United States and was employed in many of the major trials carried in this country [8, 16]. An alternative dose schedule of 150 μg/kg for 5 days was developed by Moertel and coworkers [15]. While the toxicity of these regimens was considered adequately tolerated, it was repeatedly noted that platelet and white blood cell depressions were delayed in onset, with nadirs occurring 3–6 weeks after the initiation of therapy. This pattern of delayed and cumulative bone-marrow toxicity is remarkably similar to that observed with the chloroethyl nitrosoureas, BCNU and CCNU. In recognition of this phenomenon, the dosage schedules of these latter two agents had been adjusted to allow for prolonged periods of recovery in order to prevent serious cumulative toxicity. However, in the case of mitomycin C, it was not until 1974 that a similar prolonged intermittent schedule of administration was reported. Baker and coworkers described an overall 37% objective response rate for patients with solid tumor who received a single 20 mg/m^2 dose every 6–8 weeks [1]. This included responses in 8 out of 20 cases with upper gastrointestinal cancer. The hematologic toxicity associated with this regimen was considered acceptable. In view of the delayed nature of the toxicity, it is quite possible that our past method of daily mitomycin C administration has been inappropriate. The intermittent schedule is now being actively employed in the design of combination chemotherapy regimens employing this agent.

Recently, the use of oral mitomycin C has undergone a Phase I study. The drug was administered in gelatin capsules, at doses of 10–15 mg/m^2. All patients were fasted prior to treatment. There was considerable variability in both peak serum concentration and disap-

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0344-5704/78/0001/0073/$ 1.00

pearance curves after oral absorption. The toxic effects of mitomycin C were similar to those observed with parenteral treatment and could be correlated with the peak serum concentrations. The oral route was not recommended for further clinical investigation.

Aside from the treatment limiting bone-marrow depression, several additional clinical toxicities have been described for mitomycin C. These have included a severe inflammatory reaction at injection sites if the drug is extravasated, and acute but mild gastrointestinal disturbance consisting of anorexia, nausea, vomiting, and diarrhea.

A less frequent problem has been renal toxicity, manifested by an increased serum BUN and creatinine concentration, and histologic evidence of glomerular sclerosis [12]. This complication of treatment is usually delayed in onset, occurring several months after initiation of therapy in patients who have received large total doses. Renal toxicity appears to be less important with the intermittent schedule and doses of 10–20 mg/m^2 [18].

The therapeutic activity of mitomycin C, administered as a single agent for selected tumors, has been defined in seven major trials conducted in the United States. The overall response rate for gastric cancer is 24%. Activity has also been reported for pancreatic (18%), colorectal (18%), and breast cancer (31%), in addition to head and neck, and pulmonary malignancies. The principal limitation has been the duration of response, which has lasted only an average of three months [15].

Mitomycin C has been incorporated into several drug combinations for solid tumors. The initial programs employed the daily loading method of administration. Horton et al. have reported the use of a combination of mitomycin C, thio-TEPA, 5-fluorouracil, and fluoxymesterone administered daily to 56 patients with solid tumors [9]. Responses were observed in four out of 22 patients with colonic carcinoma, and three out of 12 cases with breast cancer. At the Mayo Clinic, combinations of mitomycin C, 5-fluorouracil, and BCNU, and mitomycin plus 5-FU were compared to 5-fluorouracil used alone in a controlled randomized trial [19]. For colorectal cancer, neither combination was demonstrated to produce objective response rates superior to that achieved using 5-fluorouracil as a single agent. In contrast, two out of five patients with gastric cancer evidenced an objective response after treatment with 5-FU (9 mg/kg/day × 5) plus mitomycin C (0.11 mg/kg/day × 5) and two out of four responded to a mitomycin C plus BCNU combination.

The combination of mitomycin C, 5-fluorouracil and cytosine arabinoside was reported by Hoshino et al. [10] to have a marked synergistic activity for the murine leukemia L-1210. Subsequent clinical studies conducted by Ota et al. [17] in Japan demonstrated a response rate of 55% in patients with gastric cancer and 60% in patients with colonic cancer. Dejager and coworkers at Memorial Hospital initiated a clinical trial with the same regimen in an attempt to confirm the activity of the combination [5]. Mitomycin C (0.04–0.08 mg/kg), 5-FU (7.5–10 mg/kg) and cytosine arabinoside (0.6 or 2.0 mg/kg), MFC, were given i.v. twice a week until the development of treatment-limiting hematologic toxicity. For 32 patients with gastric cancer there was 31% response, whereas negligible activity was demonstrated for colonic and pancreatic cancer. The role of cytosine arabinoside in the MFC combination is not known and it is possible that the activity for gastric cancer is mediated solely by 5-FU and mitomycin C.

Macdonald et al. have recently described a new combination chemotherapy program for gastric cancer, FAM, in which mitomycin C is administered by the single dose intermittent schedule [13]. The FAM regimen is administered in 9-week courses: 5-FU (600 mg/m^2) is given i.v. on days 1, 8, 28, and 35 of each cycle; adriamycin (30 mg/m^2) is administered on days 1 and 28; and mitomycin C is given as a single dose of 10 mg/m^2 on day 1 only, of each treatment course. Twenty-nine patients with advanced measurable gastric cancer have been treated and 16 (55%) have evidenced an objective response. The median duration of response is 10 months, with a range of 2+–17+ months. The median survival of the responding patients is in excess of 13 months, with 25% still alive as long as 24 months after initiation of therapy. In contrast, the median survival of the nonresponders was 2.5 months and all patients had died within 6 months. The regimen was well tolerated, with myelosuppression as the principal treatment-limiting toxicity. The median nadir white blood cell and platelet counts were 2500/mm^3 and 100,000/mm^3 respectively. There was little evidence of cumulative bone-marrow depression, with 75% of initial doses being administered after one year of treatment. The FAM regimen is now being evaluated for activity in primary adenocarcinoma of lung, with preliminary report demonstrating an objective response rate of 33%.

Wiggans et al. have utilized a combination similar to the FAM regimen for advanced pancreatic cancer. In this study, streptozotocin (1.0 gm/m^2) was administered on days 1, 8, 28, and 35 in substitution for adriamycin [20]. Ten of 23 patients (43%) achieved a partial or complete (one patient) response. The median duration of response is in excess of 6 months, with four patients alive and still in a remission state. The median survival of all patients in this series is 6 months. Patients demonstrating an objective response have a median survival in excess of 7.5 months, with a range of 3–23+ months, compared to 3 months for the nonresponding group.

In summary, mitomycin C appears to have an estab-

lished role in the treatment of gastric cancer and other solid tumors. The use of a single dose intermittent schedule has allowed for the safe and effective use of this agent in recently developed combination chemotherapy regimens.

References

1. Baker, L. H., Caoili, E. M., Izbicki, R. M., Opipari, M. I., Vaitkevicius, V. K.: A comparative study of mitomycin-C and porfiromycin. Proc. Am. Soc. Clin. Oncol. **15,** 182 (1974)
2. Carter, S. K.: Mitomycin C (NSC-26980) clinical brochure, part 3. Cancer Chemother. Rep. **1,** 99–114 (1968)
3. Comis, R. L., Carter, S. K.: Integration of chemotherapy into combined modality treatment of solid tumors. III. Gastric cancer. Cancer Treat. Rev. **1,** 221–238 (1974)
4. Crooke, S. T., Bradner, W. T.: Mitomycin-C: A review. Cancer Treat. Rev. **3,** 121–139 (1976)
5. Dejager, R. L., Magill, G. B., Golbey, R. B., Krakoff, I. H.: Combination chemotherapy with mitomycin-C 5-fluorouracil, and cytosine arabinoside in gastrointestinal cancer. Cancer Treat. Rep. **60,** 1373–1375 (1976)
6. Ferguson, D., Humphrey, E.: Mitomycin C. Cancer Chemother. Rep. **8,** 154 (1960)
7. Frank, W., Osterberg, A. E.: Mitomycin C (NSC-26980), an evaluation of Japanese repots. Cancer Chemother. Rep. **9,** 114–119 (1960)
8. Godfrey, T. E., Wilbur, D. W.: Clinical experience with mitomycin C in large infrequent doses. Cancer **29,** 1647–1652 (1972)
9. Horton, J., Olson, K. B., Gehrt, P., Spear, M.: Combination therapy with 5-fluorouracil (NSC-19893), mitomycin (NSC-26980), vincristine (NSC-67574), and thioTEPA (NSC-6396) for advanced cancer. Cancer Chemother. Rep. **49,** 59–61 (1965)
10. Hoshino, A., Kato, T., Amo, H.: Combination chemotherapy of mitomycin-C, 5-fluorouracil and cytosine arabinoside in L-1210 mouse leukemia. In: Proceedings of the 10th International Cancer Congress, Houston, Texas. Clark, R. L. (ed.), pp. 409–410. Houston: Medical Arts Publishing Co. 1970
11. Jones, R., Jr.: Mitomycin C. A preliminary report of studies of human pharmacology and initial therapeutic trial. Cancer Chemother. Rep. **2,** 3–7 (1959)
12. Liu, K., Mittleman, A., Sproul, E. E., Elias, E. G.: Renal toxicity in man treated with mitomycin-C. Cancer **28,** 1314–1320 (1971)
13. Macdonald, J., Schein, P., Ueno, W., Wooley, P.: 5-Fluorouracil, mitomycin-C, and adriamycin – FAM: A new combination chemotherapy program for advanced gastric carcinoma. Proc. Am. Soc. Clin. Oncol. **17,** 264 (1976)
14. Manheiner, L. H., Vital, J.: Mitomycin-C in the therapy of far-advanced malignant tumors. Cancer **19,** 207–212 (1966)
15. Moertel, C. G., Reitemeier, R. J., Hahn, R. G.: Mitomycin C therapy in advanced gastrointestinal cancer. J. Am. Med. Assoc. **204,** 1045–1048 (1968)
16. Moore, G. E., Boss, I. D. J., Ausman, R., Nadler, S., Jones, R., Jr., Slack, N., Rimm, A. A.: Effects of mitomycin C (NSC-26980) in 346 patients with advanced cancer. Eastern clinical drug evaluation program. Cancer Chemother. Rep. **52,** 675–684 (1968)
17. Ota, K., Kurita, S., Nishimura, M.: Combination therapy with mitomycin-C (NSC-26980), 5-fluorouracil (NSC-19883), and cytosine arabinoside (NSC-63878) for advanced cancer in man. Cancer Chemotherap. Rep. **56,** 373–385 (1972)
18. Ratanatharathorn, V., Cadnapaphorndai, P., Rosenberg, B., Baker, L. H., Taber, S., Ruffer, B. W., McDonald, F. D., Vaitkevicius, V. K.: Clinical and pathologic study of mitomycin-C nephrotoxicity: A retrospective analysis. Proc. Am. Soc. Clin. Oncol. **18,** 293 (1977)
19. Reitemeier, R. J., Moertel, C. G., Hahn, R. G.: Combination chemotherapy in gastrointestinal cancer. Cancer Chemother. Rep. **30,** 1425–1428 (1970)
20. Wiggans, G., Smythe, T., Ueno, W., Macdonald, J., Schein, P., Flannery, E.: Streptozotocin, mitomycin, and 5-fluorouracil, SMF, chemotherapy for advanced pancreatic carcinoma: Phase II trial. Proc. Am. Soc. Clin. Oncol. **18,** 304 (1977)

Received September 28, 1977