Treatment of Implanted Peritoneal Cancer in Rats by Continuous Hyperthermic Peritoneal Perfusion in Combination with an Anticancer Drug

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ABSTRACT

To study the feasibility of combined hyperthermic and anticancer drug treatment for peritoneal cancer, we devised a continuous hyperthermic peritoneal perfusion system in combination with mitomycin C. The model uses i.p.-transplantable rat ascites hepatoma 100B cells. Hyperthermic peritoneal perfusion alone or combined with mitomycin C was performed after i.p. inoculation of the tumor cells into rats. In rats treated with combined peritoneal perfusion (41.5°) and mitomycin C, the mean survival times were significantly prolonged as compared to those of rats treated with peritoneal perfusion at 41.5° alone. Our results suggest that combined hyperthermic peritoneal perfusion and mitomycin C treatment may represent a therapeutic and prophylactic treatment for peritoneal metastasis after gastric cancer surgery in humans.

INTRODUCTION

A major problem after surgery for advanced gastric cancer is peritoneal metastasis which is the most frequently encountered recurrence pattern (5, 6). Despite the recent advances in anticancer chemotherapy, at present, no satisfactory treatment is available for peritoneal metastasis. There is a renewed interest in the efficacy of hyperthermia in human cancer therapy, and this treatment has now been clinically introduced. To study the feasibility of combined hyperthermic and anticancer drug therapy for peritoneal metastasis, we devised a CHPP in combination with anticancer chemotherapy. We now report its efficacy in the treatment of rats receiving i.p. transplants of rat ascites hepatoma (AH100B) cells.

MATERIALS AND METHODS

Tumors and Animals. AH100B cells, obtained from the Sasaki Institute (Tokyo, Japan), were maintained by serial passage in the peritoneal cavity of 180- to 220-g male Donryu rats. These tumor cells can be implanted peritoneally and, on the average, they cause death in 17.6 days after i.p. inoculation.

CHPP. Under general ether anesthesia, the rats were placed in the supine position (Chart 1). A midline incision was made in the upper part of the abdomen, and Silicone tubes (6.0-mm outside diameter; 4.0-mm inside diameter) were placed in the pelvic and right and left subphrenic cavities for infusion and discharge of heated rat physiological salt solution (mEq/liter: sodium, 141; potassium, 4; chlorine 103; HCO₃, 42; and glucose, 200 mg/100 ml), respectively. Then the incisional abdominal wound was closed. The perfusate was heated in a tube coil in a thermostatically regulated water bath and infused into the peritoneal cavity through a tube attached to a pump (25 ml/min for 60 min). The infused solution was discharged through tubes in the right and left subphrenic cavities. Thermistor probes, attached to a thermistor thermometer (Nippon Koden Co., Tokyo, Japan), were placed into the inflow and outflow tubes at the entrance to the abdominal cavity and into the rectum. The temperature of the infused solution could be maintained at ±0.3° (S.D.) of the selected treatment temperature. The temperature of the infused and discharged solutions and the rectal temperature are shown in Table 1. The kinetics of heat-up was similar for each target temperature, and the desired outflow temperatures were obtained a few minutes after the start of hyperthermic perfusion. After CHPP treatment, the abdominal opening was sutured. All rats were anesthetized for the entire duration of perfusion and were perfused for 60 min.

RESULTS

When rats that had received tumor-cell inoculations 1, 5, or 10 days earlier were treated with CHPP at 37°, or with CHPP at 41.5° plus MMC, none died within 48 hr of this treatment. However, 14 of 24 (54%) rats died when CHPP was at a temperature of 42.5° in the absence of MMC. In this study, we did not attempt to ascertain the cause and mechanism of death.

Survival data after CHPP treatment are shown in Table 2. The mean survival time of Group 1 (37° hyperthermia; no MMC) was not prolonged as compared to that of the controls. In Group 2 (41.5°; no MMC), the mean survival time at 10 days after tumor cell inoculation was slightly prolonged; a similar observation was made for Group 3 rats which received CHPP treatment 1 day after tumor cell inoculation. When rats were treated with CHPP at any of the 3 heating temperatures 5 days after the inoculation, their mean survival time was shorter than that of the controls. All Group 3 rats which received CHPP treatment at 10 days postinoculation died. In Group 4, those rats which received CHPP plus MMC at 1 or 10 days postinoculation manifested a significant prolongation of their survival time compared to Group 5 (MMC alone) and control rats. No prolongation of the mean survival time was observed in Group 5. At 60 days after tumor cell inoculation, the number of survivors was significantly higher in Group 4 than it was in Group 2. Sixty-day survivors were killed...
Synergistic Effect of CHPP and MMC for Peritoneal Cancer

and, upon necropsy, no peritoneal tumor cell implantation was seen macroscopically or microscopically. Chart 2 shows the survival curves after CHPP and/or MMC treatment.

DISCUSSION

Since tumor tissue is more heat-sensitive than normal tissue, hyperthermic therapy has been introduced to treat patients with certain tumors. The administration of anticancer drugs may further enhance the effect of heating on tumor tissue (1, 3, 7, 8, 11, 13, 14).

Teicher et al. (12) reported that almost no synergistic effect of heat and MMC on EMT6 tumor cells was observed in the hyperoxic condition; however, this effect was marked in hypoxic cells. Hirai (4) observed that the growth of Ehrlich cell tumors in mice or VX2 cell tumors in rabbits was markedly inhibited by the combined treatment with local heating and MMC. We evaluated the effect of this combined treatment on AH100B cells implanted in rat peritoneum, using this as a model of peritoneal metastasis in human gastric cancer. In the clinical situation, selection of the proper heating temperature is most important. In our series, the death rate in animals subjected to CHPP at 42.5° was relatively high, suggesting that prolonged CHPP treatment at temperatures exceeding 42.0° may not be tolerated by the host. The death rate in rats subjected to 41.5° CHPP treatment was low; however, no marked prolongation of the survival time was achieved by this therapy. On the other hand, when 41.5° CHPP was combined with MMC treatment, a significant prolongation of the survival time was observed. This suggests that combined CHPP and MMC treatment results in a prolongation of the survival time by a synergistic effect, even at a temperature at which, in the absence of the drug, no prolongation of the survival time was obtained. Euler et al. (2), who used rats with ascites

Table 2
Survival data after CHPP

<table>
<thead>
<tr>
<th>Hyperthermic treatment with or without MMC</th>
<th>Time (days) after inoculation</th>
<th>Mean survival time (days)</th>
<th>No. of survivors at 60 days</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (37.0°)</td>
<td>1 (n = 5)</td>
<td>14.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5 (n = 7)</td>
<td>17.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10 (n = 4)</td>
<td>16.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group 2 (41.5°)</td>
<td>1 (n = 9)</td>
<td>19.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5 (n = 8)</td>
<td>18.6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10 (n = 7)</td>
<td>&gt;24.3</td>
<td>1</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>1 (n = 6)</td>
<td>&gt;61.5</td>
<td>2</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td>5 (n = 4)</td>
<td>&gt;14.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10 (n = 4)</td>
<td>&gt;80.9</td>
<td>2</td>
<td>26.0</td>
</tr>
<tr>
<td>Group 4 (41.5° + MMC, 1 mg/kg)</td>
<td>1 (n = 7)</td>
<td>&gt;88.8</td>
<td>2</td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td>5 (n = 10)</td>
<td>&gt;63.3</td>
<td>2</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>10 (n = 10)</td>
<td>&gt;102.6</td>
<td>4</td>
<td>40.0</td>
</tr>
<tr>
<td>Group 5 (MMC, 1 mg/kg)</td>
<td>1 (n = 5)</td>
<td>&gt;19.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5 (n = 5)</td>
<td>&gt;18.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10 (n = 5)</td>
<td>&gt;18.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control group (tumor cell inoculation only)</td>
<td>17.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*a Significant difference from Group 2 (p < 0.05; x² test).
tumors (Yoshida sarcoma, Walker carcinosarcoma, and Jensen sarcoma), reported that their median survival time was prolonged slightly and that their survival rates were increased by peritoneal perfusion at 41° and 43°. Shiu and Fortner (9) observed a statistically significant improvement in the survival of rats given peritoneal implants of Morris hepatoma cells when they were subjected to i.p. hyperthermic treatment (43.3° for 30 min). Spratt et al. (10), who treated a peritoneal cancer patient (pseudomyxoma peritonei) with combined hyperthermia (42.0°) and anticancer drugs (methotrexate and thiopeta), encountered no major complications.

Thus, i.p. hyperthermic perfusion in combination with anticancer drug administration may represent an effective treatment method for human peritoneal cancer. Efforts should be directed at devising an instrument for the controlled heating of the perfusate and the selection of the optimal anticancer drug. We are now performing CHPP in combination with MMC administration in the treatment of gastric cancer patients with peritoneal metastasis. Our findings on the efficacy of this treatment will be reported in the near future.

REFERENCES


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