A Comparison of 5-Fluorouracil Administered by Slow Infusion and Rapid Injection

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SUMMARY

A comparison of 5-fluorouracil administered by rapid i.v. injection versus 2-hr infusion was conducted in a double-blind study of 149 patients with advanced large bowel cancer. Dosages for each regimen were selected to produce definite but clinically tolerable toxicity. Toxicity pattern, objective response, and symptomatic response were essentially equal with these methods of administration. For practical reasons the rapid injection method is preferred.

INTRODUCTION

The fluorinated pyrimidines, 5-FU and its deoxyriboside FUdR, have for over a decade been accepted as standard chemotherapeutic agents for treatment of patients with advanced gastrointestinal cancer. They have also had a role in the treatment of a number of other solid tumors. The toxicity of these agents, as they were initially used, was frequently quite severe, and in early reports a substantial death rate related to drug toxicity was frequently recorded. More recently, most investigators have used these agents in regimens associated with decreased toxicity, apparently without significant loss of therapeutic effect. One means of reducing toxicity has been to maintain the traditional rapid i.v. injection technique but to use a lower total dosage than originally advocated. Another has been to change the duration of administration. It has been clearly evident, since the initial studies by Sullivan et al. (3), that if the rate of administration of 5-FU is slowed a larger total dose must be used to obtain comparable levels of toxicity, whereas the opposite is true with slow infusion of FUdR.

Primarily on the basis of the presumption that slow infusion techniques would expose more cancer cells during a drug-susceptible phase of their cycle, a number of investigators have suggested that this method may offer some therapeutic advantage. This presumption, however, has never been established as fact by controlled study. We felt that the thesis of an improved therapeutic ratio for slow infusion methods could be established only by comparison with the rapid injection method in which dosage schedules for each regimen produced comparable levels of toxicity over a comparable total period of administration. Since investigations by Hall et al. (1) demonstrated that neither the time of infusion nor the vehicle had any perceptible effect on objective response rate, we elected to study slow infusion of 5-FU over a 2-hr period administered in 5% dextrose and water. For comparison, we chose a moderate dosage schedule of rapid-injection 5-FU that in our hands produces mild but definite toxicity in the majority of patients treated. To avoid any influence of bias on the part of the investigators, we felt that a double-blind technique was essential.

MATERIALS AND METHODS

All 149 patients chosen for study had histologically confirmed metastatic, unresectable adenocarcinoma of the large bowel. All were ambulatory outpatients and all were maintaining a reasonable state of nutrition prior to entry. No patient had had previous therapy with either 5-FU or FUdR, and none had had radiation or chemotherapy of any kind for at least 1 month prior to entry. Each patient had a measurable area of known malignant disease to serve as an objective indicator of response to therapy. Discrete lesions on chest X-ray, cutaneous lesions, or palpable masses clearly measurable with a ruler or caliper were considered acceptable. Lesions demonstrable only by contrast roentgenography or lesions for which size could only be estimated, e.g., pelvic masses, were not accepted. If hepatomegaly due to cancer was used as an indicator lesion, it was required that hepatic metastasis be proven by biopsy and that a clearly defined liver edge extend at least 5 cm below the costal margin on quiet respiration.

Each patient received both a daily rapid-push i.v. injection and a daily 2-hr infusion of 5% dextrose in water. The rapid-push injection was administered immediately after start of the infusion. By random assignment, either 5-FU was given in the injection and placebo (0.9% NaCl solution) in the infusion or placebo in the injection and 5-FU in the infusion. This single assignment was for both courses of therapy and for all 5 days of each course. Neither patients nor investigators were aware of this assignment until the entire study was completed and results were prepared for statistical analysis. By this method each patient received a daily 2-hr infusion of 5% dextrose in water, and the only difference in regimens was the rate of administration of 5-FU.

The dosage schedule for rapid i.v. injection was 13.5 mg/kg/day for 5 consecutive days (total dose, 67.5 mg/kg). On the basis of a pilot study, we had estimated an equitoxic dose by 2-hr infusion to be 20 mg/kg/day for 5 days (total dose, 100 mg/kg). After our initial 40 patients had been entered, our statistical section broke the code with regard to toxicity only.
Because toxicity for the slow infusion method was very mild and less than that for rapid injection, the daily dose for slow infusion was raised to 25 mg/kg/day (total dose, 125 mg/kg) for the remainder of the study.

All patients who could tolerate further treatment received a 2nd course of therapy at 5 weeks. Dosage for this course was readjusted with the object of producing definite but clinically tolerable levels of toxicity.

Evaluation of therapeutic results was conducted at 10 weeks after initiation of the 1st course of therapy. An objective response was declared if there was a reduction of at least 50% in the product of the largest perpendicular diameters of the most clearly measurable area of known malignant disease chosen prior to entry as a primary indicator lesion. If hepatomegaly was the indicator lesion, it was required that there be a reduction of at least 30% in the sum of measurements below the xyphoid and below each costal margin at the midclavicular lines without any deterioration of liver function tests (glutamic-oxaloacetic transaminase, alkaline phosphatase, and serum bilirubin). If there was increase in size of any other areas of malignant disease or if new areas of malignant disease appeared, the result was considered a treatment failure.

**RESULTS**

In the assessment of results of this study, all patients were considered evaluable if they were randomized to the study and received their 1st dose of 5-FU. If patients died before completion of their planned therapy or became too sick to continue therapy, they were tabulated as treatment failures.

Toxicity. The gastrointestinal and mucocutaneous toxicity experienced by the 2 patient groups to their 1st course of therapy is shown in Table 1. The differences in toxicity spectrums are minor, with slightly increased stomatitis in the group receiving 5-FU by rapid injection and slightly increased diarrhea, dermatitis, and cosmetically significant alopecia in the group receiving 5-FU by slow infusion. The frequency and severity of leukopenia (Table 2) is essentially the same for the 2-hr infusion at 25 mg/kg/day for 5 days and for rapid injection at 13.5 mg/kg/day for 5 days. There were 2 drug-related deaths with slow infusion and one with rapid injection.

**Therapeutic Response.** The objective and symptomatic response rates observed at 10 weeks are recorded in Table 3. They are essentially identical. There were no significant differences in therapeutic responses in patients treated by infusion with 20 or 25 mg/kg/day by 2-hr infusion dosages and patients treated by rapid i.v. infusion with 13.5 mg/kg/day.

**DISCUSSION**

In Table 4, we have listed a number of dosage regimens of 5-FU and FUdR that in our hands have produced approximately equivalent levels of definite but clinically tolerable toxicity. When one increases the duration of administration of 5-FU from a single large bolus to 10 days of 24-hr infusion, the total tolerable dose can be increased from 35 to 200 mg/kg. Conversely, when the duration of administration of FUdR is slowed, the dose must be reduced dramatically (2).

In an earlier study (2), we have demonstrated that slow infusion of FUdR results in a significant reduction of therapeutic effectiveness, probably because the early development of severe stomatitis and esophagitis precludes reaching an effective antineoplastic dose level.

In this study of 5-FU, it appears that manipulation of rate of administration in no way alters the effect on tumor or the effect on host. Both the moderate-dose rapid injection

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### Table 1

<table>
<thead>
<tr>
<th>Gastrointestinal and mucocutaneous toxicity</th>
<th>2-hr infusion (% of 75 patients)</th>
<th>Rapid injection (% of 74 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomitig</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Stomatititis</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Dermatititis</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Hematological toxicity: leukopenia</th>
<th>2-hr infusion for 5 days</th>
<th>Rapid injection for 5 days,</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>20 mg/kg/day (% of 20 patients)</td>
<td>25 mg/kg/day (% of 55 patients)</td>
</tr>
<tr>
<td>Degree of leukopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4000/cu mm</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>&lt;2000/cu mm</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>&lt;1000/cu mm</td>
<td>5</td>
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schedule and the slow infusion schedule are tolerable regimens for outpatient practice. Because of the inconvenience and increased cost entailed in slow infusion, however, practical considerations should give preference to the rapid injection method.

REFERENCES

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