A Clinical Study of 5-Fluorouracil*

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The importance of several pyrimidines in nucleic acid metabolism has made the investigation of their chemical analogs of interest to cancer chemotherapy. Recently, Heidelberger and co-workers (3) synthesized a group of fluorinated pyrimidines and pyrimidine precursors which have been shown to have anti-tumor activity in several animal tumor systems. McIver (6) et al. studied 5-fluorouracil (FU) clinically and observed severe leukopenia, thrombocytopenia, and gastrointestinal side effects in several patients. Curreri and his associates (2) also reported a few patients whose tumors decreased in size following the administration of FU. Because of the interest in this class of compounds, a pharmacologic study of FU in man was undertaken in patients with advanced neoplasia in an attempt to find a suitable dosage schedule by which one might inhibit tumor growth in man with minimal toxicity. The results in regard to toxic manifestations and antitumor activity are reported here.

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MATERIALS AND METHODS

PARTICIPATING HOSPITALS AND INVESTIGATORS

The study was conducted by the members of the Eastern Solid Tumor Cancer Chemotherapy Study Group which operates under the auspices of the Cancer Chemotherapy National Service Center (CCNSC). The hospitals and responsible investigators are listed in Table 1.

<table>
<thead>
<tr>
<th>Participating Institutions, Investigators, and Patients Studied</th>
<th>No. patients</th>
</tr>
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<tbody>
<tr>
<td>Georgetown Medical Division</td>
<td>D. C. General Hospital</td>
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<tr>
<td>Drs. B. I. Shnider* and Raul Oviedo</td>
<td>31</td>
</tr>
<tr>
<td>Jackson Memorial Hospital, Miami, Florida</td>
<td>21</td>
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<tr>
<td>Drs. R. Jones* and Jacob Colsky</td>
<td>11</td>
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<tr>
<td>Johns Hopkins Hospital, Baltimore, Maryland</td>
<td>16</td>
</tr>
<tr>
<td>Drs. A. H. Owens, Jr. and Louis Lasagna*</td>
<td>128</td>
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<tr>
<td>Lemuel Shattuck Hospital, Boston, Mass.</td>
<td>16</td>
</tr>
<tr>
<td>Drs. T. C. Hall*</td>
<td>29</td>
</tr>
<tr>
<td>T. C. Chalmers*, and M. M. Dederick</td>
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<td>National Cancer Institute, Bethesda, Maryland</td>
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<tr>
<td>Drs. G. L. Gold*, C. O. Brindley, E. T. Frei, III, and C. G. Zubrod†</td>
<td>128</td>
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<td>Roswell Park Memorial Institute</td>
<td>20</td>
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<tr>
<td>Drs. O. Selawry and J. F. Holland*</td>
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<td>Cancer Chemotherapy National Service Center</td>
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<tr>
<td>Marvin A. Schneiderman, Consultant Biostatistician</td>
<td>128</td>
</tr>
</tbody>
</table>

TOTAL

* Responsible investigator.
† Study group chairman.

PATIENTS

One hundred twenty-eight patients with proved malignancies were studied. The tumors were classified by location and histology and are listed in Table 2. The clinical status of the patients ranged from ambulatory to bedridden, and early in the course of the study a number of seriously ill patients were included whose subsequent deaths were not considered due to drug therapy.

1 Ninety per cent of the patients included in the study had measurable disease.
Drug

FU was manufactured by Hoffmann-La Roche, Inc., and provided by the CCNSC. The drug for intravenous use was prepared in ampules, stored at room temperature, and used undiluted in single daily doses. Drug stability was tested by the manufacturer during the study period. There was no evidence of significant deterioration, as judged by the amount of free fluorine present. The degree of drug-induced hematopoietic depression appeared similar during the various parts of the study period, a further evidence of drug stability. The orally administered FU was supplied in powder form and made into 100-mg., 25-mg., and 10-mg. tablets. The tablets were given as a single daily dose, in the fasting state.

**Laboratory Data**

White blood cell (WBC) counts, platelet counts, and hemoglobin concentrations or hematocrits were obtained at least twice weekly on hospitalized patients and once weekly on out-patients. Blood chemical determinations, urinalyses, electrocardiograms, and electroencephalograms were obtained at intervals to assess renal, hepatic, cardiac, and central nervous system function.

**Mechanics of Study**

At monthly meetings and biweekly telephone conferences, all the investigators were apprised of the group's experience, and further plans were made jointly.

**Definition of Terms**

A. Toxicity

1. Mild: (either a, b, or c)
   a) Hematologic—a diminution of WBC or platelet count below 5000/cu mm and 100,000/cu mm, respectively, without the occurrence of infection or bleeding.
   b) Gastrointestinal—the appearance of nausea, vomiting, diarrhea, or oral ulcerations.
   c) Alopecia.

2. Moderate: a combination of 1a and 1b.

3. Severe: a diminution of WBC count or platelet count below 5000/cu mm and 50,000/cu mm, respectively, with occurrence of infection or bleeding; or, where the drug was thought to have hastened the demise of the patient.

B. Antitumor effect

Tumor masses were measured serially by calipers or x-ray. Decrease in size of measurable tumor mass or masses at a time when no other lesions were advancing was the only acceptable criterion of antitumor effect.

**Discontinuance of Therapy**

Drug was stopped at the earliest sign of hematopoietic depression or gastrointestinal side effects attributable to FU.

**RESULTS**

**Toxicity**

*Daily intravenous schedules.*—Four, 6, or 8 mg/kg/day of FU were given to patients for a period of 14-42 days. In Table 3, the results obtained at these three dose levels are shown. Of the 25 courses of FU given to 22 patients at 4 mg/kg, 40 per cent evoked toxicity, primarily mild in degree, although two patients manifested severe toxicity. One patient showed severe bloody diarrhea after 3 weeks of drug administration. Necropsy revealed ulcerative lesions of the large bowel. The other patient showed severe leukopenia after 6 days of study, and at the time of her death a WBC count was 900/cu mm.

Thirty-four courses at 6 mg/kg were given to 29 patients (see Table 3). Approximately 80 per cent of these showed toxicity, mostly mild in degree, but more pronounced than at 4 mg/kg. One patient showed a skin eruption, thought to be related to FU, on the 27th day of therapy. Nine courses were terminated because of moderate toxicity. Two courses were stopped because toxicity became severe; one patient died with a WBC count of 500/cu mm and severe diarrhea,
while another patient with a hypoplastic bone
marrow succumbed to infection, 6 days after a
17-day course of FU.

Twenty courses at 8 mg/kg of FU were given
to seventeen patients. Seventy per cent of the
patients showed toxicity, and more than half of
these were in the moderate and severe categories.
One patient died of pneumonia 14 days after
a 12-day course of FU. He had sustained a marked
degree of thrombocytopenia, leukopenia, and diar-
rhea. Another patient received two courses of
8 mg/kg, the first lasting 9 days and the second
lasting 19 days, with a 6-day interval between
courses. He died with a WBC count of 2500/cu
mm, depressed platelet count, and had shown
painful oral ulcerations.

The average onset of gastrointestinal toxicity
occurred at 14 days, while average hematologic
toxicity occurred at 20 days.

Daily oral schedules.—The toxicity seen by the
oral route was somewhat less than that with
intravenous administration. Six patients received
seven courses of 4 mg/kg per day of FU, and only
two showed mild hematologic toxicity. Twelve
patients received fourteen courses at 6 mg/kg
per day; five experienced mild toxicity, and three
showed moderate toxicity. Twelve patients re-
ceived fourteen courses at 8 mg/kg; eight showed
mild toxicity and only one moderate toxicity (see
Table 3). The average time of occurrence of gas-
trintestinal side effects was 17 days, while hem-
atologic toxicity occurred at an average of 21 days.

TABLE 3
TOXICITY DATA OF PATIENTS RECEIVING DAILY DOSE SCHEDULES

<table>
<thead>
<tr>
<th>Dose Schedule</th>
<th>No. Patients</th>
<th>Courses</th>
<th>Total No.</th>
<th>Toxicity</th>
<th>No. Toxicity</th>
<th>Anti-tumor Effects</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>25</td>
<td>10</td>
<td>2 0</td>
<td>GI-1</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>34</td>
<td>29†</td>
<td>2 9</td>
<td>GI-10</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>20</td>
<td>14</td>
<td>3 6</td>
<td>GI-4</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

* GI = gastrointestinal; Hem = hematologic as defined in text.
† One patient who developed a drug eruption is not listed in the toxicity categories.

TABLE 4
TOXICITY DATA OF PATIENTS RECEIVING INTERMITTENT INTRAVENOUS SCHEDULES

<table>
<thead>
<tr>
<th>Dose Schedule</th>
<th>No. Patients</th>
<th>Total No.</th>
<th>Toxicity</th>
<th>No. Toxicity</th>
<th>Anti-tumor Effects</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–15 mg/kg</td>
<td>21</td>
<td>15</td>
<td>0 1</td>
<td>GI-10</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>16–34 mg/kg</td>
<td>8</td>
<td>8</td>
<td>0 0</td>
<td>GI-10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12 mg/kg</td>
<td>22</td>
<td>15</td>
<td>7 1</td>
<td>GI-10</td>
<td>7</td>
<td>1</td>
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</table>

* GI = gastrointestinal; Hem = hematologic, as defined in text.
Intermittent intravenous schedules.—Twenty-one patients received one or more doses of 10–15 mg/kg at 7-day intervals. More than two-thirds of these showed mild or moderate toxicity, mostly gastrointestinal (see Table 4).

Eight single doses of 16–84 mg/kg were given, and all patients showed signs of toxicity after a single dose. Toxicity was primarily mild and hematologic in nature (see Table 4).

The final group of 22 patients received 15 mg/kg per day for 5 days. This regimen was repeated every 8 days, provided the hematologic and gastrointestinal status of the patient permitted. Three patients received three or more courses, six received two courses, and thirteen patients only one such course of FU. Seven patients showed mild toxicity, six hematologic and one gastrointestinal. Depression of the formed elements of the blood occurred about 2 weeks after the drug was started. Seven patients manifested severe toxicity. The five deaths that occurred in this group were attributed to administration of drug, and all but one patient had marked depression of thrombocytes and leukocytes. This patient died 5 hours after the fifth dose of drug. At autopsy, extensive metastatic carcinoma was found, but no immediate anatomic cause of death was discovered.

Aside from the toxic manifestations mentioned above, four patients showed alopecia. This was associated with hematologic depression. Abnormalities seen in the hair roots were morphologically similar to those described with severe methotrexate intoxication. (7)

Anti-tumor effects

Of the 128 patients treated, eight showed objective evidence of tumor regression (see Appendix), but most of the responses were transient in nature. Of the eight responses seen, it is of interest to note that only one patient showed severe toxicity, while the majority showed minor degrees of toxicity.

DISCUSSION

Our data corroborate those of Curreri et al. (2) and Ansfield and Curreri (1) in regard to the types of toxicity seen most frequently with FU, i.e., hematologic and gastrointestinal disturbances. Also, we have observed alopecia similar to that seen with antifolic compounds. We are also in agreement with the findings of others (4) that FU is absorbed from the gastrointestinal tract. The particularly high incidence of severe toxicity seen with large intermittent doses without apparent increase in anti-tumor effect is of interest, since Liebling and co-workers (5) found intermittent FU therapy in mice less effective than daily therapy.

It was disappointing to find toxicity at all doses of drug used, and limited anti-tumor activity despite the use of maximally tolerated doses. Rothberg has collected data from several investigators and demonstrated a similar lack of favorable responses to FU in eighteen patients with advanced acute leukemia, many of whom were carried to toxicity. It seems unlikely that FU will contribute significantly to the therapy of cancer patients.

SUMMARY

1. In the dose schedules used, 5-fluorouracil showed toxicity sufficient to cause discontinuation of the drug when given in daily intravenous doses of 6 mg/kg or higher or interrupted intravenous doses larger than 15 mg/kg weekly.

2. The orally administered compound was less toxic and could be given with reasonable safety in doses of 8 mg/kg daily for 6 weeks.

3. The drug produced a low rate of objective anti-tumor responses at dosage levels which were fairly toxic, and no relationship between anti-tumor effect and toxicity was apparent.

APPENDIX

Case 70.—A 67-year-old negro male was admitted with epidermoid carcinoma of left tonsil and cervical metastases. He had been previously treated with x-ray therapy and 6-azauracil. He was started on 6 mg/kg of FU by mouth on 1-4-58 and continued through 4-17-58 without signs of toxicity. There was regression in the size of the metastatic lesions, one decreasing 40 per cent in size and another diminishing from 3.5 cm × 2.2 cm. to less than 1 sq. cm. The regression was transient, and at the end of the study both lesions were the same size as at the onset.

Case 63.—A 60-year-old negro female with adenocarcinoma of the rectum and hepatic metastases, presented with right upper quadrant fullness, anorexia, and weight loss of 2 months' duration. She was treated with 5-fluorouracil orally on a daily schedule of 8 mg/kg. At the end of the study, both the hepatic and rectal lesions were unchanged and the patient was still doing well.

1 Personal communication.
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duration. Physical examination revealed a large nodular liver, one nodule measuring 16.2 cm. X 12 cm. Study with FU was begun on 2-20 and continued until 2-28 at a dose of 4 mg/kg, given intravenously. There was no toxicity, and her general status greatly improved. She was discharged on 1-25-58 and was placed on FU, 10 mg/kg weekly, I.V., on 1-26-58. At the time of discharge the hepatic mass measured 10 cm. X 7.5 cm. Shortly before the patient's death on 2-18-58, the mass began to increase in size.

Case 15.—A 47-year-old white male was found to have osteolytic lesions of the right ilium in January, 1958. He was treated with local x-ray therapy after a diagnosis of undifferentiated carcinoma was made by bone biopsy. He was admitted to the hospital on February 17, 1958, because of bone pain. Physical examination revealed firm bilateral axillary lymphadenopathy 2 cm. in diameter and tenderness in lower thoracic and lumbar spine, right hip, and iliac regions. X-rays revealed destruction of right ilium, involvement of right femoral greater trochantar. FU, 15 mg/kg daily, I.V., for 5 days was begun on 2-20. The patient developed severe toxicity, but the axillary nodes completely regressed. Patient developed pneumonia that responded to antibiotics, but did poorly, sustaining a pathological fracture of hip on 8-17. He received FU, 4 mg/kg daily, I.V. for 42 days. During this time his cough decreased, and his measurable tumor masses decreased 25 per cent in size. A WBC count depression to 3000 was noted during the last week of study. The patient received FU, 100 mg/kg daily, I.V. for 42 days. During this time his cough decreased, and his measurable tumor masses decreased 25 per cent in size. A WBC count depression to 3000 was noted during the last week of study. The patient was not seen on a regular basis after his discharge 8 weeks following completion of the above trial. When last seen, 5 months after cessation of FU therapy, his status was unchanged. A minimal cough persisted, and the tumor mass remained unaltered. No other therapy had been given in the interim.

Case 51.—A 64-year-old negro male with inoperable bronchogenic carcinoma had been diagnosed 12 months prior to admission, and had received a course of x-ray and nitrogen mustard therapy without obvious effect. The patient received FU, 4 mg/kg daily, I.V., for 42 days. During this time his chest discomfort disappeared, and the left hilar mass decreased 50 per cent in size. During the last week of FU administration the patient developed increasingly troublesome nausea and vomiting. There was no evidence of marrow depression. Subsequent to the cessation of this course, the patient was asymptomatic and gained 8 kg. in body weight. Anorexia and chest discomfort returned 8 months later without objective change in observable tumor mass, and the patient was given FU, 800 mg. (4.4 mg/kg) daily, orally, for the next 82 weeks. During this course of drug the patient reported the disappearance of his chest pain and anorexia. No definite evidence of drug toxicity nor effect on tumor was noted.

The patient is still alive 9 months after his original trial on FU, again complaining of chest discomfort and cough. The observable tumor mass has not changed in size, since this first course of FU was completed.

Case 93.—A 57-year-old white female with metastatic breast carcinoma of 3 years' duration had been previously treated with hormones and nitrogen mustard. She received weekly intravenous injection of 15 mg/kg of FU for 11 of 13 weeks. After 10 weeks of study, the number of subcutaneous metastatic nodules diminished from 10 to 8. There was a concomitant decrease in the size of her hepatomegaly from 12 cm. to 0 cm. below the costal margin. No changes were noted in patient's extensive osseous metastatic disease. Toxicity was minimal, consisting of diarrhea and vomiting on day 28, and alopecia starting on day 56.

Case 96.—A 71-year-old white male with squamous-cell carcinoma of the tongue underwent surgery in 1957, followed by radiation therapy. On 1-11-58 intravenous FU, 6 mg/kg daily, was begun but stopped after 18 days because of diarrhea. Drug was re instituted 2 days later. A decrease in size of all four lymph nodes being measured was observed transiently, but regrowth occurred during the 5th week of study.

Case 90.—A 40-year-old negro female had a hysterectomy for leiomyosarcoma of the uterus in 1954. The tumor recurred locally, and in September of 1956 a posterior pelvic exenteration was done. In February of 1957 the first pulmonary metastasis was demonstrated in the left upper lung field. She received FU, 8 mg/kg daily, orally, from 1-2 to 1-16-58. The drug was stopped because of nausea and vomiting which cleared in a few days. On 2-4, the FU was restarted at 8 mg/kg daily, orally, and continued until 2-17, when it again had to be stopped because of nausea and vomiting. One lung lesion which had been steadily increasing in size by serial x-rays over the preceding 10 months decreased from 5.6 cm. X 4.8 cm. on 12-24 (1 week before start of therapy) to 5.0 cm. X 4.0 cm. on 3-3, 8 weeks after the drug was stopped. No new metastases appeared during this time.

ACKNOWLEDGMENTS

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REFERENCES


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