Sequential l-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC 79037) and 5-Fluorouracil (NSC 19893) Therapy of Gastrointestinal Cancer

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SUMMARY

Thirty-six patients with advanced gastrointestinal carcinoma were treated sequentially with full therapeutic doses of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea followed by 5-fluorouracil. 5-Fluorouracil could be safely administered at 6 weeks although patients still demonstrated peripheral hematological depression secondary to the earlier 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea therapy. Of the 36 patients, 8.3% showed an objective response to 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea therapy. Of the 21 patients who were able to receive sequential 5-fluorouracil, 19% showed objective response. Only 8.3% of all patients entered into this trial showed objective response after completion of the sequential therapy, and this program must be judged as ineffective treatment for gastrointestinal cancer.

INTRODUCTION

Single-agent chemotherapy with our current pharmacological armamentarium has, in the main, produced disappointing clinical results for gastrointestinal cancer. Traditional use of multiple drugs in this class of neoplasm has been to initiate therapy with a 2nd agent only after the patient has failed to show objective response to the 1st or, having showed it, has later shown escape. With this approach, the patient is treated with the 2nd agent at a more advanced stage of his disease, when his general condition and ability to tolerate chemotherapy have probably deteriorated, and also when any useful antineoplastic effect from the initial agent has been irretrievably dissipated.

An alternative approach has been to administer 2 or more cytotoxic drugs simultaneously. With most currently available agents, however, this requires reducing the dose of each constituent member of the combination to less than an optimal level to avoid intolerable additive hematological toxicity. In trials with simultaneously administered combinations of mitomycin C, 1,3-bis(2-chloroethyl)-1-nitrosourea, and 5-FU,2 we could detect no improvement in antineoplastic effect in comparison to any of these agents used alone (4).

On the basis of favorable results with animal tumor models achieved at the Southern Research Institute and the Ontario Cancer Institute, and principles of sequential chemotherapy have been enunciated by others (1, 3, 5). This approach has involved the use of 2-chemotherapeutic agents in sequence, either 2 cell-cycle-nonspecific agents or a cell-cycle-nonspecific agent followed by a cell-cycle-specific agent. Both drugs are used at optimal doses, and the 2nd drug in the sequence is administered as soon as possible after the 1st to obtain a maximal reduction in total viable tumor cells. Using this method with sequential cyclophosphamide and 6-mercaptopurine, Laster et al. (3) observed a high cure rate in advanced mouse adenocarcinoma 755 when no cures could be obtained with either agent used alone.

The clinical experiment reported here was designed to apply the principle of sequential chemotherapy to patients with advanced gastrointestinal cancer by use of a cell-cycle-non-specific alkylating agent, CCNU, in sequence with a possibly cell-cycle-specific antimetabolite, 5-FU. These particular drugs were chosen because each has been shown in our experiments to have some activity against gastrointestinal adenocarcinoma.

MATERIALS AND METHODS

Patient Selection. Thirty-six patients with advanced and metastatic gastrointestinal cancer were selected for study. The sites of the primary lesions are listed in Table 1. Thirty-five patients had adenocarcinoma, and 1 had an undifferentiated carcinoma of the esophagus. All had positive histological confirmation of unresectable carcinoma, and all had measurable areas of known malignant disease to serve as objective indicators of response to therapy. Each patient was ambulatory and maintaining a reasonable state of nutrition. Twenty-one patients had received no previous cytotoxic drugs, while 15 had received previous treatment with 1 or more agents: 10 with camptothecin, 5 with 5-(3,3-bis(2-chloroethyl)-1-triazeno)-imidazole-4-carboxamide, and 2 with emetine. Eight patients had received previous roentgen therapy. None had received either radiation or chemotherapy within 1 month of entry on the study. All patients were informed that they were participating in a clinical experiment to evaluate a new chemotherapy approach.

CCNU Treatment. CCNU was always given as the 1st drug

1 Supported by Grant NIH 70-2066 from the National Cancer Institute, NIH, Bethesda, Md.
2 The abbreviations used are: 5-FU, 5-fluorouracil; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea.

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and administered according to the method described by Hansen et al. (2). A single p.o. dose of 130 mg/sq m was given after a 4-hr fast. Patients were premedicated with 25 mg of prochlorperazine by rectal suppository in an effort to forestall emesis. White blood counts were obtained twice weekly and platelet counts were obtained weekly for 6 weeks thereafter.

**5-FU Treatment.** At 6 weeks, all patients whose general condition permitted were treated with 5-FU. In 7 patients, this treatment was deferred from 1 to 2 weeks because of the necessity for treatment of active infection, severe anemia, or other problems complicating their malignant disease or their initial CCNU therapy. Treatment was not deferred, however, for leukopenia or thrombocytopenia, since Hansen et al. (2) have shown that at 6 weeks the bone marrow has recovered from CCNU toxicity, even if this is not yet reflected in the peripheral counts.

5-FU was administered by rapid i.v. injection at a dose of 13.5 mg/kg/day for 5 consecutive days. Therapy was discontinued earlier if the patient developed any specific evidence of 5-FU toxicity, i.e., stomatitis, dermatitis, or diarrhea. Leukocyte counts were obtained twice weekly for 3 weeks after initiation of 5-FU therapy.

Patients were evaluated for objective response at 6 weeks after CCNU therapy and at 4 weeks after initiation of 5-FU therapy. Cycles of therapy were repeated for all patients who showed objective response or who remained objectively stable if their general condition permitted.

**RESULTS**

**Toxicity.** The significant toxic reactions to CCNU are documented in Table 2. These are comparable to the reports of others and our own earlier observations with this agent.

Of the 36 patients entered in this study, 21 were able to receive sequential therapy with 5-FU. Their toxic reactions are shown in Table 3. These also are consistent with our previous experience with 5-FU in this dosage schedule. The leukopenia secondary to 5-FU was not excessive, in spite of the fact that many of these patients were treated when there was still a significant peripheral leukocyte depression from their earlier CCNU therapy.

**Objective Response.** Our criteria for objective response were a reduction in the product of the longest perpendicular diameters of the most clearly measurable area of known malignant disease by at least 50% or, if malignant hepatomegaly was the indicator, a reduction by 30% in the sum of measurements below the xiphoid process and both costal margins at the midclavicular lines during quiet respiration. There could be no increase in size of other areas of malignant disease, and no new areas could appear.

The symptomatic and objective responses at 6 weeks after initial CCNU therapy are shown in Table 4. The 8.3% regression rate is less than in our earlier experience with CCNU, but the difference is not statistically significant. The symptomatic and objective responses at 4 weeks after initiation of 5-FU therapy, expressed in relationship to measurements at the initiation of 5-FU therapy, are shown in Table 5. The 19% regression rate is essentially the same as in our previous experience with 5-FU given by intensive course and is perhaps in the lower range of those reported by others.

In Table 6, the therapeutic response is shown as assessed at 10 weeks and after 1 full cycle of sequential CCNU and 5-FU therapy. These are expressed in relationship to the patients' status at onset of 5-FU therapy.
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Table 6
Sequential CCNU and 5-FU therapy

<table>
<thead>
<tr>
<th>Symptomatic (% of 36 patients)</th>
<th>Objective (% of 36 patients)</th>
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<tbody>
<tr>
<td>Improved</td>
<td>28</td>
</tr>
<tr>
<td>Stable</td>
<td>3</td>
</tr>
<tr>
<td>Worse</td>
<td>69</td>
</tr>
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status at entry into the study preceding the administration of the 1st dose of CCNU. There were no additional responses with continued cycles of therapy in patients who were objectively stable at 10 weeks, nor was there any subsequent improvement in quality of response in those patients who had showed regression at 10 weeks.

DISCUSSION

Certainly the 8.3% objective response rate achieved at 10 weeks cannot be categorized as anything more than a dismal failure for sequential CCNU and 5-FU therapy in gastrointestinal cancer. By no means, however, can this result be interpreted as a condemnation of the principle of sequential therapy as it might be applied to other neoplasms or with other drugs for this class of neoplasm.

In retrospect, it would seem that CCNU was a less than ideal choice for the initial drug in this sequential study. Although it has some activity against gastrointestinal adenocarcinoma, the magnitude of this activity is of a very low order. Also, because of the delayed toxicity of CCNU, the 2nd drug in the sequence could not be safely administered until 6 weeks had elapsed. At this time, 72% of the patients had shown progression of their malignant disease; more than one-third had deteriorated to a point that further chemotherapy could not be given; and many of those who received 5-FU were in less than optimal general condition.

It would seem advisable that future trials of sequential therapy be designed with an initial drug in the sequence that has a high order of therapeutic effectiveness or that dissipates its hematological toxicity quickly so that the secondary drug can be administered without inordinate delay.

REFERENCES

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