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A Phase 2 Study of Intermittent High-Dose Cyclophosphamide Therapy of Advanced Gastrointestinal Cancer[1]

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SUMMARY

Thirty-two patients with advanced gastrointestinal carcinoma were treated with intermittent high-dose cyclophosphamide on a schedule of 30 to 40 mg/kg by rapid i.v. injection given every 3 weeks. Nine patients overall and 8 of 17 previously treated patients showed objective tumor regression. These responses, however, were too transient to be accorded any clinical value.

INTRODUCTION

Cyclophosphamide is a marketed chemotherapeutic agent that has been in clinical use for many years. It has found usefulness either alone or in drug combinations for the treatment of a number of specific neoplasms and seems to have a curative potential for Burkitt's tumor. In view of these credentials it is quite remarkable that this agent has never had anything approaching an adequate Phase II trial in gastrointestinal cancer. Among 5 different small studies reviewed by Livingston and Carter (1) there were 47 colorectal patients treated with cyclophosphamide by various schedules, and the rates of objective response varied from 0 to 25%.

The purpose of our investigation was to evaluate the therapeutic potential of intermittent high-dose cyclophosphamide in advanced gastrointestinal adenocarcinoma and particularly in colorectal carcinoma.

MATERIALS AND METHODS

Patient Selection. Thirty-two patients were chosen for study: 18 males and 14 females. All had histologically confirmed metastatic, unresectable adenocarcinoma with primary neoplasms in the gastrointestinal tract. The mean age was 56.4 years; the range was 34 to 70 years. The specific sites of the primary cancers for these patients are listed in Table 1. The previous treatment for their advanced malignant disease is documented in Table 2. All were ambulatory outpatients, all were maintaining a reasonable state of nutrition, and all had normal leukocyte and platelet counts. No patient had had either radiation or chemotherapy of any kind for at least 1 month prior to entry on our study. Therapy was also delayed for at least 1 month after any major abdominal surgical procedure. 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 demonstrated 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 a metastasis be proven by biopsy and that a clearly defined liver edge extend at least 5 cm below the costal margin on quiet respiration.

Cyclophosphamide was dissolved in 5% dextrose in water and administered by rapid i.v. injection. Calculation of dosage was based on actual or ideal weight, whichever was less. Dosage for our 1st 10 patients was 40 mg/kg. Because of excessive hematological toxicity, the remaining 22 patients were treated at an initial dosage of 30 mg/kg. Patients were advised to drink fluids liberally for 24 hr preceding treatment, and following treatment they were advised to drink a full glass of water every hour and to pass urine every hour. If there was any question about the patient's ability to maintain adequate fluid intake by mouth, parenteral fluids were administered. Following treatment, leukocyte and platelet counts were obtained twice weekly. If the patient's general condition permitted, treatment was repeated at 3 weeks and at 6 weeks. Dosage for subsequent treatment was reduced if excessive toxicity was experienced with initial courses. If at 9 weeks the patient showed objective regression of his malignant disease or if his condition had remained objectively stable without clinical deterioration, treatment was continued at 3-week intervals until progressive disease was evident.

Patients were reevaluated with measurement of indicator lesions at 3-week intervals. An objective response was declared if there was a decrease by at least 50% in the product of the longest perpendicular diameters of the most clearly measurable area of known malignant disease chosen prior to therapy as the primary indicator lesion. There could be no increase in other areas of known cancer and no new lesions could appear. If malignant hepatomegaly was chosen as an indicator, it was required that there be a decrease by at least 30% of the sum of measurements below the xyphoid process and each costal margin at the midclavicular lines without deterioration of liver function tests (serum bilirubin, glutamic oxaloacetic transaminase, and alkaline phosphatase).

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RESULTS

Toxicity. The overall toxicity experienced by our patients is listed in Table 3. Although vomiting was frequent, it was generally mild and persisted only during the day of treatment. Hemorrhagic cystitis was experienced by only 2 patients. Thrombocytopenia was mild, transient, and never life-threatening. The dose-limiting toxic effect was leukopenia. The leukocyte count reached a nadir at a median of 13 days with a range of from 8 to 18 days. Recovery was generally prompt. In Table 4 we have shown the relative frequency and severity of leukopenia at our dosage levels of 40 and 30 mg/kg. Most patients seem to tolerate the latter dose quite well, but the severity of leukopenia at a dosage of 40 mg/kg would seem to exceed limits of clinical tolerability.

With 2nd and 3rd courses there was evidence of cumulative bone marrow injury (Table 5) in more than one-half of our patients. In addition to more severe leukopenia, the duration of leukopenia was also extended, and several patients did not show complete recovery of peripheral counts when they returned at 3 weeks.

Therapeutic Response. The objective response in our patients to intermittent high-dose cyclophosphamide therapy is shown in Table 6. The rate of response, particularly in untreated patients, was surprisingly high. Regrettably, however, these responses were very transient. Only 3 were maintained for 9 weeks and all patients showed progressive disease at 12 weeks. The responses are broken down according to specific neoplasms in Table 7. Data are really adequate only for large bowel cancer, but it is of interest that 3 of 4 patients with gastric carcinoma showed objective improvement.

Table 1

Sites of primary carcinomas of patients treated

Sites	No. of patients with tumor
Large bowel	25
Stomach	4
Cholangiocarcinoma	1
Hepatoma	1
Islet cell	1

Table 2

Previous treatment

Treatment	No. of patients
None	17
Chemotherapy	14
5-fluorouracil	12
5-azacytidine	4
Camptothecin	1
Streptozotocin	1
Radiation	7

Table 3

Toxic reactions following cyclophosphamide therapy in 32 patients

Toxic reaction	% of patients
Nonhematological	
Vomiting	78
Hemorrhagic cystitis	6
Alopecia	37
Hematological	
Leukopenia	
4,000/cu mm	84
Thrombocytopenia	
150,000/cu mm	23
100,000/cu mm	3
50,000/cu mm	

Table 4

Cyclophosphamide therapy: initial dosage and degree of leukopenia

Lowest WBC/cu mm	40 mg/kg (% of 10 patients)	30 mg/kg (% of 21 patients)
<4000	90	81
<3000	80	67
<2000	70	29
<1000	40	9.5

Table 5

Cyclophosphamide therapy: nadir of leukopenia with 2nd course at same dose

Leukopenia	No.
No change	7
25-50% lower	4
>50% lower	4

Table 6

Objective (>50%) response to cyclophosphamide therapy

Duration of response in patients was: 3 weeks, 4 patients; 6 weeks, 2 patients; 9 weeks, 3 patients.

	No. of patients	%
Overall	9/32	29
No prior chemotherapy	8/17	47
Prior chemotherapy	1/15	7

Table 7

Response of specific neoplasms to cyclophosphamide therapy

Primary carcinoma	No prior drug treatment	Prior drug treatment
Large bowel	5/13	0/12
Stomach	2/2	1/2
Cholangiocarcinoma	1/1	
Hepatoma	0/1	
Islet cell		0/1

DISCUSSION

It is evident from the results of this study that intermittent high-dose cyclophosphamide does have antineoplastic activity in a significant proportion of patients with gastrointestinal cancer. Unfortunately, the duration of this effect is so transient that this mode of therapy cannot be accorded any practical clinical role. It is possible, however, that high-dose cyclophosphamide could serve as a useful induction agent in sequential chemotherapy regimens.

REFERENCES

1. Livingston, R. B., and Carter, S. K. Single Agents in Cancer Chemotherapy, p. 34. New York: Plenum Publishing Corporation, 1970.