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Phase II Trial with Chlorozotocin in Advanced Colorectal Cancer*

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Abstract—*The single agent activity of chlorozotocin was evaluated in advanced colorectal cancer not previously treated with chemotherapy. The drug was given at a dosage of* 200 mg/m^2 *i.v. repeated every* 6 wk. *Of* 23 *evaluable patients,* 2 *achieved a partial response lasting* 4 *and* 5 *months respectively. With this dosage regimen, chlorozotocin produced essentially nausea and vomiting in one-half of the patients as well as myelosuppression that varied with performance status. Our findings suggest that the therapeutic index of chlorozotocin is similar to that of other conventional nitrosourea derivatives in this disease. However, additional experience is needed to definitely assess how cumulative is their respective bone marrow toxicity.*

INTRODUCTION

CHLOROZOTOCIN is a newly synthetized water-soluble 2-chloroethyl analog of the methyl nitrosourea, streptozotocin [1]. It differs from BCNU by the substitution of a glucose carrier for the chloroethylnitrosourea cytotoxic group. The drug exerts curative antitumor activity in the L1210 murine leukemia that is comparable to that achieved with BCNU [2]. However, at optimal therapeutic doses in this experimental system, the decrease in white blood cells is profound with BCNU but only minimal with chlorozotocin [2]. A striking difference in myelosuppressive activity between chlorozotocin and BCNU has also been suggested in studies testing the sensitivity of human CFU-C to equimolar concentrations of these drugs [3].

Chlorozotocin produces DNA damage in L1210 leukemia cells by cross-linking [4]. Kinetic responses of sensitive cells to the drug appear to be similar to those generally reported with other chloroethylnitrosoureas with greater cytotoxicity for noncycling cells than for cycling cells [5].

Talley *et al.* performed a broad phase II study with chlorozotocin given by i.v. bolus at a dose of 90–120 mg/m^2 every 6 wk [6]. No response was noted among 34 patients with colorectal cancer. However, the vast majority of these patients had received prior chemotherapy. In addition, minimal toxic effects were encountered suggesting that a suboptimal dose of the drug had been selected for this trial. This was further substantiated by phase I findings of Taylor *et al.* indicating that phase II evaluation of chlorozotocin should be undertaken at a dosage of 200–225 mg/m^2 for the single-dose schedule [7]. Of note, in both trials, drug-induced myelosuppression appeared to be much less cumulative relative to what might be observed with BCNU, CCNU or methyl CCNU.

These observations prompted us to perform a phase II evaluation of chlorozotocin given at a dose close to the maximum tolerated dose. The trial was conducted in patients with advanced colorectal cancer not previously treated with chemotherapy.

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MATERIALS AND METHODS

All patients had histologically confirmed colorectal carcinoma and measurable lesions. The disease was always recurrent or metastatic and no longer suitable for radiation therapy. Patients with a performance status of <40 on the Karnofsky scale were not eligible for the study. Other eligibility criteria included WBC ≥ 4000/mm^2, platelet counts ≥100,000/mm^3, serum creatinine ≤1.5 mg/100 ml, and serum bilirubin ≤2.0 mg/100 ml. Previously irradiated lesions could not be used to evaluate the antitumor effect of chlorozotocin. Patients who received prior chemotherapy were not eligible.

Chlorozotocin was supplied by Simes S.p.a., Milano as a white dry powder in vials containing 100 mg of drug. Chlorozotocin was reconstituted with absolute alcohol and sterile water for injection. The resulting solution was administered as a single injection over 15 min in 150 cc of dextrose 5% in water at a dosage of 200 mg/m^2 repeated every 6 wk. The study protocol called for dose reduction if WBC ≤2000/mm^3 and/or platelets ≤75,000/mm^3 were observed in the previous course.

Follow-up studies included WBC and platelet counts every week during the first course of therapy and every other week thereafter. Hepatic and renal function tests were scheduled prior to each course.

Antitumor effect was assessed every 6 wk. Complete response was defined by the disappearance of all clinically detectable tumor. Partial response was a reduction of at least 50% of the sum of the products of the longest perpendicular diameters of the clearly measurable lesions. There could be no increase in any other indicator lesions and no appearance of any new areas of malignant disease. Response duration was calculated from the commencement of drug therapy.

RESULTS

Of 26 eligible patients entered in the trial, 23 were evaluable for assessing antitumor activity of chlorozotocin. Two patients were excluded from this analysis for inadequate follow-up and one for death occurring within 4 weeks from initiation of therapy. Pretreatment characteristics of the evaluable patients are summarized in Table 1. There were 13 men and 10 women with a median age of 60 yr and a median performance status of 80 on the Karnofsky scale. Most patients had been previously treated with surgery alone or with radiotherapy. One patient had received one 4-day course of 5-fluorouracil at initiation of radiotherapy and was considered eligible for this trial. Indicator lesions were essentially located in the liver and the lung.

The number of courses per patient varied from 1 to 4. Thirteen patients had one course, seven had 2 courses and three had 3 or 4 courses. Two patients experienced partial remission. They achieved definite tumor shrinkage in an abdominal mass and a cutaneous lesion for 4 and 5 months respectively.

Overall, the drug was very well tolerated. The most important toxic effect was myelosuppression consisting of leucopenia and thrombocytopenia. Among 13 patients who had at least 5 weekly blood counts per course, the median WBC nadir was 3800 cells/mm^3 and the

Table 1. Pretreatment characteristics

Total evaluable	23
Men:women	13:10
Age: median	60
range	27–88
Performance status (Karnofsky): median	80
range	50–100
Prior surgery	14
Prior surgery and radiotherapy	6
Prior chemotherapy*	1
No prior treatment	2
Site of indicator lesions	
Liver	8
Lung	7
Abdominal mass	3
Skin	1
More than 1 site	4

*One 4-day course of 5-fluorouracil at initiation of prior radiotherapy.

Table 2. Drug-induced myelosuppression

	No. of patients	Nadir WBC × 10^3/mm^3		Nadir platelets + 10^3/mm^3	
		Median	Range	Median	Range
All patients	13	3.8	1.3–6.9	100	20–185
Karnofsky 80–100	7	4.7	1.0–6.9	105	20–185
Karnofsky 50–70	6	2.4	1.3–4.5	47	20–133

median platelet nadir was 100,000/mm^3 (Table 2). The corresponding median days of nadir were 38 (range: 16–45) and 23 (range: 18–31) respectively. Bone marrow toxicity noticeably varied according to performance status (Table 2). There was no indication of cumulative myelosuppression with repeated courses but the number of evaluable courses per patient was too limited to truly assess cumulation. Infection developed in three patients and possibly contributed to death in one of these who was 88 yr old. Bleeding was seen in two patients but was at least partially related to hypersplenism in one.

Mild to moderate gastrointestinal intolerance consisting of nausea and vomiting was seen in 12 patients. Diarrhea occurred in 3 patients. Other nonhematological toxic effects consisted of alopecia, stomatitis, and apparently drug-related cystitis which were seen in one patient each. Renal, hepatic, pulmonary or other toxic effects were not encountered.

DISCUSSION

Chlorozotocin is a new nitrosourea derivative which seems clinically similar to BCNU, CCNU and methyl CCNU. This new drug may also achieve antitumor activity in advanced colorectal cancer. Although the small number of patients in this study is not sufficient to define a response rate with accuracy, it would appear that its antitumor activity in this disease is very close to what may be expected with other nitrosourea derivatives [8].

Overall, chlorozotocin seems to be very well tolerated. Gastrointestinal toxic effects consisting mostly of nausea and vomiting are generally of minimal clinical significance. The drug produces essentially bone marrow toxicity with late leucopenia and earlier thrombocytopenia. The degree of myelosuppression encountered with the dose schedule that we have used varies widely from one patient to another. A dosage of 200 mg/m^2 seems suitable for phase II studies in patients with good performance status (PS 80–100) and with no prior chemotherapy although myelosuppression may be occasionally severe in this group of patients. Lower performance status is probably an indication that this dosage should be reduced. Our data are consistent with findings of others suggesting that hematologic toxicity is less cumulative with chlorozotocin than with BCNU, CCNU, or methylCCNU. These observations favor chlorozotocin relative to these other nitrosourea derivatives, but additional investigations are still needed to confirm this important advantage.

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