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Acknowledgements—The authors appreciate the excellent secretarial skills of Karen A. Smith and Catherine Thompson and the expert data management of Catherine Janus.

This study was supported in part by grant #CA-06927 from the National Cancer Institute.

Eur J Cancer, Vol. 27, No. 12, pp. 1593–1596, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Infusion of Floxuridine plus Etoposide plus Cisplatin in Human Malignancies

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36 patients with advanced malignancy were studied in a phase I trial of continuous 24-h infusion of floxuridine (FUdR) plus etoposide plus cisplatin (FEP) administered for 5 consecutive days at 4-week intervals. Study design fixed the dose rate of etoposide and cisplatin with escalation of FUdR only. Dose rate-limiting toxicity related to the FUdR component was stomatitis and diarrhoea and was invariably associated with leukopenia and thrombocytopenia when grade 3 or 4 level gastrointestinal toxicity was observed. Only 3 of 64 courses were associated with transient renal failure related to cisplatin. Drug-related deaths occurred (leukopenia-associated sepsis) in 4 patients with poor performance status (ECOG 3 and 4). Responses occurred in 15 of 26 evaluable patients (all previously treated minimally or untreated) including 5/11 non-small cell lung cancer; 3/3 oesophageal; 2/2 breast; 4/5 gastric; 1 osteogenic sarcoma; and 1 unknown primary (probably ovary). The recommended dose rates for a 5-day infusion of the three agents for good risk patients is 20 mg/m² per day of each drug. For poor risk patients including age > 65 years; performance status 2 or greater; or extensive bone metastases or prior radiation; the recommended starting dose rates are: FUdR 15 mg/m² per day; etoposide 15 mg/m² per day; and cisplatin 20 mg/m² per day. Dose escalation of FUdR to a maximum of 25 mg/m² daily is feasible in selected patients demonstrating optimal tolerance.
Eur J Cancer, Vol. 27, No. 12, pp. 1593–1596, 1991.

INTRODUCTION

ETOPOSIDE HAS been combined with platinum in an infusion for 24 h in two phase I trials which established the optimal dose rate for 3 [1] or 5 [2] day infusion of the two agents for a total dose of 150–225 mg/m² for etoposide and 90–100 mg/m² for platinum. The two drug combination has demonstrated synergism in experimental systems and, in addition, the mechanism of action of each of the drugs is distinctive; etoposide representing a plant alkaloid inhibits topoisomerase and platinum is a non-classical alkylating agent.

We undertook a phase I–II clinical trial adding a third agent in the form of a classical antimetabolite to the mixture. Floxuridine (FUdR) was selected on the basis of its established compatibility with platinum and a previous phase I trial in which floxuridine was admixed with platinum [3]. In addition, the initial two studies of the etoposide/platinum combination had demonstrated activity in gastric cancer a tumour for which the fluoropyrimidines in general and FUdR in particular has demonstrated some activity [4].

PATIENTS AND METHODS

Eligibility for entry into the clinical trial required an established histological diagnosis of advanced malignancy. The tumours must have had established resistance to standard therapeutic modalities or the malignancy was one for which no standard effective chemotherapeutic regimen existed. All patients must have had a life expectancy of at least 4 weeks to insure adequate evaluability. Additional prerequisites included: performance status by ECOG scale of 3 or less; white blood count of 3500/μl or more; platelet count of 125 000/μl or more; and creatinine clearance of greater than 50 ml/min. Patients must have completed at least a 4 week interval off chemotherapy if they had received prior chemotherapy of any kind and must have provided written informed consent as required by the Institutional Review Boards.

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Revised 10 July 1991; accepted 26 July 1991.

Drug compatibility

The compatibility of cisplatin with etoposide has been previously reported. The incompatibility of 5-fluorouracil with platinum has also been previously described. FUdR was reconstituted to provide an initial projected starting dose of 3 mg/m^2 per day. The three agents were mixed in 1000 ml of normal saline and the drug mixture sampled on day 1, 3, 5 and 7 with the solution maintained at room temperature. High pressure liquid chromatography (HPLC) analyses were carried out on the samples in duplicate. Etoposide and FUdR maintained the concentration identified at days 1–7 and no new peaks indicating a change in the character of the solution appeared [5].

Mixture formulation

Each of the three drugs was reconstituted according to the manufacturer's specifications. Each individually calculated daily dose was then dissolved in a total volume of physiological saline equal to 1000 ml per each 10 mg/m^2 of cisplatin. The maximum volume per day was 2000 ml of physiological saline; each litre was supplemented with 20 mmol/l of KCl and 12.5 g of mannitol.

Study design and dose escalation scheme

The dose rate for etoposide and cisplatin was fixed at 30 mg/m^2 per day and 20 mg/m^2 daily, respectively for 5 consecutive days. Cycles were planned to be repeated every 28 days. FUdR was the single agent planned for escalation with a starting dose of 3 mg/m^2 per day. 3 patient entries were anticipated at this level and 1 mg/m^2 per day was the planned escalation for each level anticipating diarrhoea to be the dose rate-limiting toxicity. At FUdR dose rates of 3–6 mg/m^2 per day in a total of 26 courses, only a singular incidence of grade III gastrointestinal toxicity was observed. This minimal frequency of toxicity and the report by Moertel *et al.* from 1971 [6] indicating that that the optimal dose rate for a 5-day infusion of FUdR would be in the range of 2 mg/kg per day and prompted a restructuring of the dose escalation scheme after 12 patient entries. At FUdR 2 mg/kg per day for 5 days of continuous infusion the dose rate/m^2 would be projected to be in the range of 70 mg/m^2/day. The new dose escalation scheme for the three drug mixture manipulating only FUdR was initiated at 10 mg/m^2 per day dose initial patient entries and escalation proceeded to 15, 20, 25 and 30 mg/m^2 per day.

Dose modification was introduced for patients developing bone marrow toxicity after the initial course if there was a clinical indication for subsequent treatment based on tumour assessment. In patients demonstrating a response to the first cycle and in whom grade 4 leukopenia or thrombocytopenia developed, subsequent cycles were administered with a reduction of etoposide and FUdR to two thirds of the initial dose rate. The platinum dose rate remained unchanged as long as renal function returned to normal.

Patient monitoring

All treatment courses were administered on an inpatient basis. A complete blood count and serum creatinine and liver function tests were obtained on the day of discharge and weekly between cycles. Weekly contract was provided to monitor gastrointestinal effects which may have been delayed. For patients with evaluable tumours by radiographical studies, the appropriate radiographs were obtained at monthly intervals.

Toxicity criteria

Grading of toxicity followed the modified format of the Eastern Cooperative Oncology Group and the Mid-Atlantic Oncology Program. Table 1 outlines the criteria employed for haematological and gastrointestinal toxicity and stomatitis.

Tumour response criteria

Response criteria followed the modified criteria of the Mid-Atlantic Oncology Program. A complete response indicated a complete regression of all objectively measurable tumours and an improvement in performance status by at least one grade. Partial response indicated a 50% reduction in the product of the perpendicular diameters of all measurable lesions by palpation or radiographical measurements. Patients were considered evaluable for response only if there was an objectively measurable lesion and the patient had received at least two cycles of therapy.

RESULTS

A total of 36 patients were entered and received 64 treatment courses which were evaluable for toxicity. The number of courses received by individual patients ranged from 1 to a maximum of 4 (Table 2). The median age was 59 (range 36–85) years. 20% of patient entries were over the age of 70. The distribution of entry by performance status indicates that one third of the patients were in ECOG categories 3 or 4, although entry criteria required no greater than performance status 3. The tumour types were dominated by non-small cell lung cancer and upper gastrointestinal cancer including both oesophagus and stomach.

Toxicities were separated into two broad categories. Gastrointestinal toxicity included both stomatitis or oral mucositis as well as diarrhoea or enteritis. The gastrointestinal effects were presumed to be related to the FUdR almost exclusively, since previous reports of etoposide and cisplatin administered as a two drug mixture over 5 days reported these effects infrequently or not at all. At FUdR doses of 15 mg/m^2 daily or less, gastrointestinal toxicity was observed in only 3 of 43 treatment courses (Table 3). Beginning at 20 mg/m^2 per day, clinically important gastrointestinal effects were observed in a substantial proportion of patients. Of the 21 courses administered at 20, 25, or 30 mg/m^2 per day, 9 were associated with grade 3 or 4 toxicity. These numbers represent 33%; 75%; and 40% of the patients entered, respectively at 20, 25 and 30 mg/m^2 daily. Analysis of the 4 patients developing grade 4 toxicity revealed that all 4 were within a poor risk category. 3 of the 4 were 75 years old or greater and one had received extensive prior radiation therapy.

Stomatitis was invariably associated with enteritis, although the severity of the stomatitis generally exceeded that of the enteritis. The gastrointestinal effects were also associated with some degree of bone marrow suppression and the severity of the gastrointestinal effects correlated with the severity of the leukopenia and/or thrombocytopenia.

The second major dose rate-limiting toxicity for the three drug combination was bone marrow suppression presumably primarily related to the etoposide component of the regimen, and to a lesser extent the FUdR. Although the experimental design of the phase I study dictated a fixed dose rate for etoposide at 30 mg/m^2 per day, patients developing bone marrow suppression and demonstrating evidence of response were dose-adjusted for this component with subsequent cycles. The distribution of dose rates of etoposide administered is indicated in Table 4. 51 of the 64 courses were administered at the prescribed

Table 1. Toxicity criteria

	Grade 1 Minimal	2 Moderate	3 Severe	4 Life-threatening	5 Lethal
Haematological					
WBC ($\times 1000/mm^3$)	3.0–3.9	2.0–2.0	1.0–1.9	<1.0	
Platelets ($\times 1000/mm^3$)	90–125	50–89	25–49	<25	
Gastrointestinal					
Diarrhoea	Watery no therapy	Watery requires therapy	>5×/d	Requires intravenous hydration	
Stomatitis	Transient no therapy	>5 days requires therapy	>7 days <10% weight loss	<10% weight loss, requires hospitalisation	

Table 2. Patient and clinical trial characteristics

Clinical feature	Number of patients
Total entry	36
Treatment courses	64
Age median	59
Range	36–85 years
Performance status	
0–1	16
2	8
3–4	12
Tumour types	
Lung	13
Gastric	5
Oesophageal	4
Breast	2
Sarcoma	2
Pancreatic	2
Other*	8
Prior therapy	
Chemotherapy	5
Radiation	5
Both	6
None	20

*Includes melanoma, ovary, endometrial, TUO, colon, bladder (2) and basal cell.

Table 3. Floxuridine dose rate-related gastrointestinal toxicity (including stomatitis and diarrhoea)

FUdR dose (mg/m^2 per day)	No. of courses	Toxicity grade 0	1	2	3	4
<10	26	25			1	
10	10	9			1	
15	7	6			1	
20	12	5	2	3	—	4
25	4	1			3	
30	5	2		1	2	

Table 4. Etoposide dose rate related bone marrow toxicity

Etoposide dose (mg/m^2 per day)	No. of courses	Toxicity grade* 0	1	2	3	4	5
30	51	35	2	5	3	3	3
20	11	3	1	1	4	2	
15	3			1	1		1

*See text for criteria for leukopenia and thrombocytopenia.

protocol dosage. Approximately 70% of the treatment courses experienced virtually no bone marrow suppression at this dose rate. 18%, however, experienced grade 3 or 4 toxicity. There were 4 drug-related deaths secondary to leukopenia-associated sepsis.

At the 30 mg/m^2 per day dose, the 3 drug-related deaths were in patients with a performance status of 4 upon review and who had received extensive prior chemotherapy. At the etoposide dose of 20 mg/m^2 per day, six of 11 courses were associated with grade 3 or 4 toxicity. 4 of the 6 patients were aged 78–80 and 1 patient had tumour occupying the bone marrow. At 15 mg/m^2 per day, a single patient experienced grade 3 toxicity; this individual was 85 years of age. A second patient had drug-related leukopenia with sepsis and died after receiving a second cycle at reduced dosage and while responding to therapy. On the basis of an acceptable bone marrow suppression frequency of 25% of patients achieving grade 3 or less toxicity and guided by risk status, the recommended dose rate for etoposide for a 5-day, three drug mixture infusion is 20 mg/m^2 per day in good risk patients as a starting dose with possible escalation to 25 mg/m^2 per day. The starting dose for poor risk patients is 15 mg/m^2 per day with a maximum escalation to 20 mg/m^2 per day.

Of the 36 patient entries, 10 patients were considered inevaluable for tumour response by virtue of receiving only a single course of therapy or the absence of a measurable lesion. Of the 26 evaluable patients, 15 demonstrated an antitumour response by objective criteria. 13 of the 15 patients were previously untreated with chemotherapy and 2 had received prior adjuvant chemotherapy for breast cancer. Reponses included 3 of 3,

oesophagus cancer; 4 of 5 gastric cancers; 2 of 2 breast cancers; and 5 of 11 non-small cell lung cancer. A response was also observed in 1 patient with metastatic osteogenic sarcoma and in a patient with unknown primary but presumed ovarian cancer.

DISCUSSION

Mixtures of antineoplastic agents represents a unique approach to multiagent chemotherapy enabling all of the agents to be administered on an infusion schedule. Phase I studies for a variety of two drug and three drug combinations involving the fluoropyrimidines and the anthracyclines have been reported [7–10]. Etoposide and cisplatin are two agents with a broad spectrum of antitumour activity which are synergistic in experimental systems and which have been reported in phase I trials as an infusion mixture for 72 and 120 h [1, 2]. The addition of FUdR to the two drug admixture of etoposide and platinum introduces an antimetabolite to the regimen with minimal overlapping toxicity and serves as the major rationale for the present phase I study of FEP.

The experimental design of the trial involved fixing the dose rate of delivery for two of the agents and escalating only the third (FUdR). The major toxicities observed involved the gastrointestinal tract (stomatitis and diarrhoea) and bone marrow suppression. For the most part, the toxicity patterns are attributed, respectively to the FUdR and the etoposide components of the regimen. Nonetheless, those patients experiencing the most severe grades of gastrointestinal toxicity generally developed bone marrow suppression as well.

The recommended dose rates for delivery of a 5-day infusion of the three components is conditioned by the patient risk category based upon performance status, age, extent of disease, and extent of prior therapy. Poor-risk patients include those over the age of 65; performance status greater than 2; and the presence of bone or bone marrow disease, extensive liver disease, or prior radiation to bone marrow-producing sites. For good risk patients, the recommended dose rate of the three drugs is 20, 20 and 20 mg/m^2 daily, respectively for FUdR, etoposide and cisplatin. For poor-risk patients, the recommeneded dose rates are 15, 15 and 20 mg/m^2 daily, respectively.

It is evident that in spite of the presumed absence of overlapping toxicity particularly in terms of bone marrow suppression, the mixture nonetheless results in a lesser cumulative dose or daily dose rate for each of the three drugs in the mixture compared to the single agent infusion dose rates particularly for etoposide and FUdR. The cisplatin dose rate appears to be totally unaffected by the addition of etoposide or floxuridine and in fact, the experience with renal failure in the 64 courses is noteworth for its rarity. Etoposide as a single agent may be safely administered at a dose rate of 60 mg/m^2 per day for a cumulative dose of 300 mg/m^2 in a 5-day infusion [11], and a dose rate of 30 mg/m^2 per day for 5 days (cumulative dose 150 mg/m^2) has been reported in a two drug mixture programme [2]. The three drug mixture reported here resulted in an optimal dose rate for etoposide of 20 mg/m^2 daily or 100 mg/m^2 cumulative dose. This represented one third of the dose administered as a single agent. For FUdR, the optimal dose rate of 20 mg/m^2 daily for 5 days was less than one third of the optimally administered dose rate when administered as a single agent for a 5-day infusion.

The present phase I trial also demonstrated clinical activity. Responses were observed in a broad spectrum of cancers including gastric and oesophageal cancer, as well as non-small cell lung cancer. Interesting also were the responses observed in breast cancer and in osteogenic sarcoma. The contribution of floxuridine to the anti-tumour effects observed clearly is indeterminant. Formal phase II trials in a broad spectrum of tumours particularly in previously untreated patients should precisely identify the clinical activity for the drug regimen and phase III comparative trials with single or double agent infusions should be carried out in sequence.

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Acknowledgement—This study was supported in part by The Cancer Center Research Foundation.