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Eur J Cancer, Vol. 27, No. 6, pp. 747–749, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Phase II Clinical Trial of Doxifluridine in Patients with Advanced Ovarian Cancer

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35 evaluable patients were treated with 5′-deoxy-5-fluorouridine (doxifluridine), a fluoropyrimidine derivative. All patients had been heavily pretreated and had refractory disease. Treatment with doxifluridine at a dosage of 3000 mg/m² given intravenously for 5 successive days at 3-week intervals led to 6 partial remissions (17%). The main side-effects were central neurotoxicity, stomatitis and myelotoxicity, resulting in 2 toxic deaths. In patients with renal function disturbances, toxicity proved to be more severe. We concluded that the drug should not be used in patients with renal impairment. Because responses have been encountered, further evaluation of the drug may be warranted in the less toxic oral form.
Eur J Cancer, Vol. 27, No. 6, pp. 747–749, 1991

INTRODUCTION

DOXIFLURIDINE (5′-deoxy-5-fluorouridine, 5′-dFUR) is a fluoropyrimidine derivative. Its chemical structure consists of a 5-fluorouracil (FU) molecule attached to a pseudopentose. In animals it has shown marked antineoplastic activity against a wide variety of leukaemias and solid tumours. Activity has been detected after both intraperitoneal [1] and oral administration [2, 3]. It has been established that, compared with other fluoropyrimidines, doxifluridine possesses a higher therapeutic index in animals [1, 2, 4].

Alberto *et al.* [5], who performed a phase I study to evaluate a daily intravenous bolus injection for 5 days, found myelosuppression and stomatitis as dose limiting factors. The maximum tolerated dose was 5000 mg/m²/day [5]. The dose recommended for further clinical use was 4000 mg/m²/day × 5 in patients without previous chemotherapy and 3000 mg/m²/day × 5 in pretreated patients, as has also been reported by others [6, 7].

We selected the drug for phase II testing not only to determine its antitumour activity but also to further characterise its toxic effects. Because the main metabolite of doxifluridine, i.e. 5-fluorouracil, is rapidly converted by the liver and because excretion is independent of renal function, we assumed that no dose adjustments were required for renal function disturbances due to prior treatment with cisplatin. This made the drug attractive for patients with a relapse of ovarian cancer who often have a renal function impairment.

MATERIALS AND METHODS

Protocol entry criteria in this non-randomised study included histologically verified epithelial ovarian cancer stage III or IV (FIGO classification); measurable or evaluable disease and documented disease progression refractory to alkylating drugs and cisplatin. 19 patients reached a partial remission on initial treatment, but showed progression before further tumour

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Revised and accepted 25 Feb. 1991.

regression could be achieved. 3 patients had a complete remission after initial treatment, but showed progression at retreatment for relapse. Patients initially treated with a cisplatin combination received cisplatin, doxorubicin, cyclophosphamide plus hexamethylmelamine (CHAP-5) or cyclophosphamide plus cisplatin (CP) [8]. Patients who received an alkylating drug up-front were retreated on relapse with a variety of cisplatin combinations: cyclophosphamide, doxorubicin, cisplatin in 3; platinum, velbe, bleomycin in 2; hexamethylmelamine, doxorubicin, platinum in 2 and CP in 1. At relapse the patients were eligible for protocol treatment. All patients, therefore, had experienced progressive disease during treatment with cisplatin and an alkylating drug.

Informed consent was obtained from the patient according to the regulations applied in the individual participating institutions. Patients were excluded if they were older than 70 or had a WHO performance status of 3 or more [9]. At the start of chemotherapy the haematological status had to be favourable (at least 3000 leucocytes/μl and more than 100 000 platelets/μl), bilirubin <30 mmol/l and serum creatinine <200 μmol/l. Previous treatment with 5-fluorouracil or any other fluoropyrimidine excluded patients, and at least 4 weeks had to have elapsed since chemotherapy; all toxic effects of prior treatment had to have been resolved. The following conditions also excluded a patient from entry into the study: brain involvement or leptomeningeal disease, previous or concurrent cancer of another side, an active uncontrolled infection, or some other non-malignant systemic disease that would render a patient a poor medical risk.

Doxifluridine was supplied by F. Hoffmann-La Roche (Mijdrecht, The Netherlands) in vials containing 1000 mg pure substance as a 10% sodium salt. Doxifluridine had to be prepared immediately before use, and the contents of vials were dissolved with 10 ml sterile water for injection.

Patients received doxifluridine in a dose of 3000 mg/m^2 on 5 consecutive days. The drug was administered in 5–10 min. Concurrent administration of a standard antiemetic was permitted. The treatment was repeated at 3-week intervals. Drug administration was postponed by 1 week if full haematological recovery from the prior course had not occurred before the scheduled retreatment (leucocytes more than 3000/μl and platelets more than 100 000/μl). The treatment could be postponed for at most 2 weeks. If full haematological recovery had still not occurred, dose adjustments were made according to the lowest value of the leucocyte and platelet counts determined on day 15. Dosage adjustments made necessary by other toxic effects were not anticipated. Patients received at least two courses to be evaluable unless it was not in their best interest. Response was assessed according the WHO criteria [9]. Patients showing disease remission continued treatment until disease progression or severe toxicity occurred. Those whose disease status remained unchanged could have treatment discontinued after 3 courses. Patients showing disease progression before the second course of therapy went off treatment but were evaluated in the category of "early progression" rather than "non-evaluable".

RESULTS

38 patients were enrolled in the study. 2 were ineligible because they had a poor performance status (WHO 3) at the start of treatment and 1 patient never received the planned treatment. The characteristics of the remaining 35 patients are shown in Table 1. A total of 121 courses were administered: 6 patients received 1 course, 10 patients 2 courses, 8 patients 3 courses, 5 patients 4 courses, and 6 patients between 5 and 12 courses of treatment. In the 121 courses of doxifluridine given, a mean of 90% of the planned dosage was administered.

Table 1. Patients' characteristics

Registered	38
Eligible	36
Evaluable	35
Age (years)	
Median	58
Range	39–69
Performance status	
0	16
1	13
2	6
FIGO stage at protocol entry	
III	25
IV	10
Histological type	
Serous	6
Mucinous	3
Undetermined adenocarcinoma	12
Undifferentiated	14
Prior chemotherapy	
CHAP-5	13
CP	12
Alkylating drugs followed by cisplatin combination	10
Results of initial chemotherapy	
Partial response	19
Clinically complete response	3
No response at all	13

No. of patients.

6 patients out of 35 had a partial remission (17%); 4 of them despite having disease progression during treatment with cisplatin. In 11 cases (31%) the disease remained stable. 11 patients were classified as having progressive disease, and 5 had early progressive disease; 2 patients died after the first course due to toxicity. One developed grade 3 stomatitis and grade 4 thrombocytopenia and leucocytopenia complicated by pneumonia and septic shock. The other probably died of cardiotoxicity (blood counts were normal and autopsy revealed no other cause of her death). Another patient died because of toxicity of subsequent treatment not related to doxifluridine. All other patients died of subsequent progressive disease.

Table 2. Side-effects according to WHO criteria

	Grade of toxicity				
	0	1	2	3	4
Nausea and vomiting	9	7	14	5	0
Diarrhoea	32	0	1	2	0
Infection	29	3	1	0	2
Oral stomatitis	22	5	4	4	0
Hair	20	7	3	3	0
Peripheral neurotoxicity	23	4	5	3	0
State of consciousness	28	6	0	0	1
Renal (blood creatinine)	25	4	6	0	0
Leucopenia	6	10	10	5	4
Thrombocytopenia	22	5	4	1	3

No. of patients.

Median survival of all patients was 6 months and that of partial responders 9 months. Toxicity according to WHO criteria [9] is presented in Table 2. Neurological complications were diverse: ataxia was seen in 8 patients, confusion in 2, depersonalisation in 5, and epileptic insults in 2 patients, in 1 case resulting in coma. Other side-effects included fatigue, abnormal gait, vertigo and dizziness. In all cases the side-effects were reversible after protocol treatment was stopped. The reason for stopping protocol treatment was progressive disease in 21 patients, death in 4 and toxicity in 10.

DISCUSSION

We observed 6 (17%) partial remissions among 35 patients with advanced ovarian cancer. All of these patients had been heavily pretreated and 4 were progressive under cisplatin treatment. These data permit the conclusion that doxifluridine has moderate efficacy in previously treated patients. The response rate is comparable to that achieved with 5-fluorouracil having a response rate of about 17% when strict objective response criteria are applied [10].

Doxifluridine is rapidly converted by hepatic and gastrointestinal tissue into 5-fluorouracil, which is immediately released into the blood. This can lead to systemic toxicity as commonly encountered after treatment with higher dosages of 5-fluorouracil. The bone marrow, which has a low phosphorylase activity, is probably sensitive to the concentration of 5-fluorouracil in the blood. The antitimour effect and mucositis may be due to a different mechanism: the intracellular transformation of doxifluridine into 5-flourouracil. In our study the neurological side-effects were the main reason for stopping treatment. Most of the neurological symptoms probably corresponded with cerebellar disturbances. These side-effects were also mentioned in two other reports [11, 12]. The neurotoxicity may be due to a direct toxicity of doxifluridine itself. Another hypothesis to explain the neurotoxic side-effects was put forward by De Bruijn *et al.* [13]. They stated that if doxifluridine can pass through the blood–brain barrier more easily than 5-fluorouracil, conversion in the central nervous system can lead to accumulation of the latter, due to the inability of this drug to re-enter the general circulation and this might then be responsible for the central nervous system toxicity [13].

12 patients included in this study have also been described in a pharmacokinetic report [13]. A correlation between the creatinine clearance, some pharmacokinetic parameters of doxifluridine, and the observed side-effects was demonstrated. Especially the patients with poor creatinine clearance showed severe toxicity, due to the unexpected impaired renal excretion of doxifluridine [13]. 3 of the cases of grade IV leucopenia were observed in patients with renal impairment, and the same holds for 2 of the 3 patients with thrombocytopenia and the 2 patients with an infection. So the drug should never be given to patients with an impaired renal function. In total, 9 patients had suboptimal renal function (creatinine between 120 and 200 μmol/l) but only 1 of these 9 patients showed a response. So it can be expected that giving it only to patients with optimal renal function will not detract the antitumour effect (5 responses in 26 patients with normal renal function). The peripheral neuropathy encountered in our study was caused by previous treatment with cisplatin and is not a side-effect of doxifluridine.

We conclude that doxifluridine should not be used in patients with renal impairment, but the present findings justify further evaluation of the drug. Alberto *et al.* [3] tested in a phase I approach an oral form of doxifluridine. Using oral administration, no neurologic or cardiac toxicity was encountered [3]. Their results suggest that for future use the oral instead of the intravenous form of doxifluridine is to be preferred.

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