Acta Oncologica Vol. 30 No. 1 1991

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DOXORUBICIN IN COMBINATION WITH VERAPAMIL IN ADVANCED COLORECTAL CANCER

A phase II trial

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Abstract

The possibility that verapamil might increase the sensibility of colorectal carcinomas to doxorubicin was studied in 24 patients without previous cytotoxic chemotherapy. The treatment started with oral verapamil, which was escalated up to the individual maximum tolerable dose (defined by prolongation of P-Q in ECG, fall in blood pressure, or dizziness). The median maximum tolerable dose was 600 mg (range 320–1 440 mg). During continued verapamil administration the patients then got weekly infusions of doxorubicin, 25 mg/m^2. The median number of doxorubicin courses was 8 (range 2–22). Among 21 patients evaluable for response and toxicity two partial remissions occurred but no complete remission. The study did not indicate enhanced cardiac, hematological or non-hematological toxicity from the combined treatment.

Key words: Colorectal carcinoma, chemotherapy, doxorubicin, verapamil.

Doxorubicin (DOX) has antineoplastic activity towards a wide range of human and experimental tumors. It is, however, a major problem that many cancers develop resistance after a few treatments or are resistant from the first presentation. The colorectal cancers belong to the resistant tumors and are nearly unaffected by treatment with DOX (1–3).

The phenomenon of resistance to DOX and other anthracyclines has been intensely studied in the last two decades and some mechanisms responsible for the drug-resistance have been found (4).

Kessel et al. (5) in 1968 showed on mouse leukemic cells that anthracyclineresistant tumor cells accumulated lower quantities of the drug than sensitive cells. A few years later Danø (6) emphasised, from studies on Ehrlich ascites tumors, that the transport of daunorubicin from the resistant cells is an active, energy-demanding process. These findings have since been confirmed by several investigators (7, 8).

Following the recognition of active drug efflux as one factor for resistance to anthracyclines, several compounds inhibiting this efflux have been studied. Among these, verapamil (VRP), a calcium influx inhibitor, was found to reverse the resistance to anthracyclines in vitro (9, 10), Chauffert et al. (11) demonstrated on colon cancer cell lines from rats, that VRP alters the cellular pharmacokinetics and enhances the cytotoxicity of doxorubicin. On the other hand VRP does not seem to potentiate the cytotoxic effects on normal bone marrow cells or fibroblasts (12, 13). So far, clinical trials combining treatment with DOX and VRP have not shown increased myelotoxicity or gastrointestinal toxicity (14–16). Ozols et al. (15) found some cardiac toxicity when using i.v. infusion of VRP at high rate.

The present report concerns a trial with weekly infusions of DOX combined with oral VRP.

Material and Methods

Patients with histologically proven advanced colorectal carcinoma entered the trial. All had measurable/evaluable disease and had not previously been treated with cytostatic drugs.

Eligible criteria were: performance status (WHO) ≤ 2, normal ECG and blood pressure, normal bone marrow

Submitted 29 September 1989.
Accepted for publication 24 March 1990.

Table 1

Patient characteristics

	No. of patients
Female	11
Male	13
Rectal cancer	6
Colon cancer	18
Median age: 53 years (range 28–71)	
Median performance status (WHO): 0 (range 0–2)	
Measurable parameters	
Localized abdominal tumor	10
Liver metastases	15
Lung metastases	6
Abdominal lymph nodes	1
Lymph nodes (clinically evaluable)	2

function, S-creatine < 150 μmol/l, normal S-bilirubin and P-alkaline phosphatase < 2 times upper normal limit. The patient characteristics are listed in Table 1.

The protocol treatment was accepted by the patients following oral and written information. The study was approved by the Danish Health Authorities and the Ethical Committee.

After informed consent was obtained, treatment was started with VRP (Isoptin, Knoll) 320 mg/day orally, which was increased by 80 mg every second day until the individual maximum tolerable dose (MTD) was reached. MTD was defined by: 1) P-Q interval in ECG prolonged, but still less than 0.22 s, 2) fall in systolic blood pressure to 90 mm Hg, or 3) dizziness related to VRP. During the escalation phase, ECG and subjective symptoms were recorded before the dose was increased. To avoid toxicity due to peak plasma levels the daily dose was split up in 3 to 4 portions taken with 8 or 6-h intervals.

After 4 days at MTD of VRP, the left ventricular ejection fraction (MUGA) was measured and blood samples for monitoring plasma levels of VRP and its metabolities were obtained. These were taken 2–4 h after the last VRP intake.

VRP and its metabolites were determined by high pressure liquid chromatography (HPLC) on a 100 × 4.6 mm MOS-hypersil column (5 μm particles) with 55% acetonitril in 35 mmol/l ammonium acetate as the mobile phase. The method followed the description by Mølgaard et al. (17), with the exception that the serum samples were extracted with diethylether and D517 was used as internal standard. The detection limit was 5 nmol/l. The variation coefficient (between series) determined at two levels, 0.15 and 1.2 μmol/l, was around 5% for all parameters (n = 18).

Weekly i.v. infusions of DOX (Adriamycin, Farmitalia-Erba) 25 mg/m^2 were then started. Physical examination, ECG and measurement of blood pressure were performed before DOX-treatment and then every fourth week. Hemoglobin, leukocytes, and platelets were measured prior to treatment and 1, 2, 3 and 6 weeks after the start of DOX infusions. These parameters were then measured every fourth week. MUGA, P-VRP, nor-VRP, chest radiography and ultrasound or CT-scan of the abdomen were repeated every eighth week of treatment with DOX. Lesions measurable by clinical examination were evaluated every fourth week. Treatment was discontinued if the patient refused treatment or if disease progression or unacceptable toxicity occurred. To avoid cardiac toxicity the patients stopped treatment with DOX at a cumulative dose of 550 mg/m^2. If the WBC was $1-2 \times 10^9$/l and/or the platelet count $75-100 \times 10^9$/l the DOX dose was reduced to 50%. If WBC $< 1 \times 10^9$/l or platelet count $< 75 \times 10^9$/l the DOX treatment was stopped. The weekly DOX-dose was increased with 5 mg/m^2 after 8 weeks of treatment if WBC $> 3 \times 10^9$/l and platelet count $> 100 \times 10^9$/l.

Results

All patients but one with ileo-rectal anastomosis needed laxative to prevent constipation during treatment with VRP. Twenty-two patients reached their individual maximum tolerable dose (MTD) of VRP. The median MTD was 600 mg (range 320 to 1 440 mg). The indications of MTD were: P-Q prolongation in ECG (n = 8), dizziness without systolic BP fall to 90 mm Hg (n = 13), fall in systolic BP to 90 mm Hg without dizziness (n = 1). Apart from the P-Q prolongation in some patients, no significant ECG changes were seen and no patients developed clinical signs of chronic heart failure. The median value of plasma verapamil at MTD before DOX treatment started was 1.44 μmol/l (n = 22, range 0.18–5.57), the median plasma nor-verapamil was 1.13 μmol/l (n = 22, range 0.36–3.99). The median value of MUGA was 59% (range 33–71) at MTD of verapamil, before DOX-treatment was started.

The median number of DOX courses was 8 (range 2 to 22). All treatments except one were administered in the outpatient clinic and superintended by a nurse. It was seldom necessary to postpone treatment or to reduce the dose due to toxicity. The median total dose of DOX was 190 mg/m^2 (range 50 to 550) and the median number of weeks of treatment with DOX were 8 (range 3 to 23).

Seven patients were treated with DOX for more than 8 weeks. In two patients the doxorubicin dose was increased by 5 mg/m^2/week.

Of the 24 patients who entered the trial, three were not treated with DOX: one patient refused cytostatic treatment, two patients were operated on for intestinal obstruction and coecal abcess respectively, and therefore never finished the VRP escalation. Twenty-one patients were treated with DOX at MTD of 7 VRP and were evaluable for response and toxicity. Two partial remissions occurred

Table 2

Number of patients experiencing toxicity

Type of toxicity	WHO grade				
	0	1	2	3	4
Leukocytes	6	4	4	6	1
Thrombocytes	21	0	0	0	0
Hair loss	4	4	1	12	0
Stomatitis	4	3	10	4	0
Nausea/vomiting	3	7	7	4	0

lasting 6 and 6+ months (response rate 10%, 95% confidence limits: 1–30%). No complete remissions occurred. Two patients had stable disease for 5+ months. The median time to progression was 9 weeks, and the median survival time 6 months.

Apart from alopecia grade 3, experienced by 57% of the patients, toxicity was generally mild (Table 2). No treatment-related deaths were seen. In general, cardiac toxicity was not observed and no patients developed clinical signs of chronic heart failure. One female patient, with a daily dose of 1 440 mg VRP, once had an Adam-Stoke's attack and was admitted to a local hospital. ECG showed nodal rhythm with a frequency of 35/min. Her daily dose was reduced by 160 mg, the ECG normalized and the dizziness disappeared. This incident was probably caused by the fact that she had taken her total daily dose in less than 8 h on that day. She continued in the study at the reduced dose for 9 more weeks. Apart from this no ECG changes were observed in any of the patients during the concomitant treatment with DOX and VRP.

The median absolute change of MUGA (n = 16) after 8 weeks of DOX-treatment was +2% (range −9 to +7).

Discussion

The combined treatment with intravenous VRP and DOX has been reported to be problematic due to cardiac toxicity (15). The design of the present trial made it possible for the patients to reach an individual maximum tolerable dose of VRP without cardiac side-effects. Despite this, the response rate was low (about 10%) and, consequently, the combined treatment is not recommendable in advanced colorectal carcinoma.

Like some other investigators (14, 16) we did not observe enhanced cardiac, hematological or non-hematological toxicity resulting from the combined treatment. Before treatment with DOX was started, the median plasma levels of VRP and nor-VRP and MTD of VRP were 1.44 and 1.13 μmol/l respectively. At this concentration level, enhanced cytotoxicity by the combined exposure to DOX and VRP has been demonstrated in P388 leukemic cells (18) and ovarian cancer cell lines (19). However, Chauffert et al. (11) needed in colon cell lines concentrations of 10 μm/l VRP for demonstration of enhanced cytotoxicity from incubation with DOX and VRP, a level about 5–10 times higher than that obtained in the present study. This might in part explain the poor therapeutic result obtained in our study. However, results from in vitro studies and clinical studies cannot be directly compared, due to great differences in the metabolism of both VRP and DOX, and in the levels of DOX to which the tumor cells are exposed over a range of time. Furthermore, the plasma level of a drug does not necessarily mirror the tumor cell concentration. The plasma levels of VRP in our two patients who responded to the treatment were 1.46 and 0.18 μmol/l. Thus, no apparent relationship between plasma level of VRP and response could be seen.

Recently, Goodman et al. (20) have shown that the ability of VRP to modulate cytotoxicity only seems to be present in tumors having developed in vivo resistance to the drug. This phenomenon might have influenced our results, as none of the patients had received previous cytotoxic chemotherapy.

ACKNOWLEDGEMENTS

The authors would like to express their thanks to Helle Bojesen-Kofoed for technical assistance and to Knoll Pharmaceutical Company, Ludwigshafen for supplying reference substances.

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