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Phase I Studies of Rodorubicin Single Bolus and Daily Times Five, Once Every Three Weeks in Patients with Advanced Solid Tumors

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Abstract—*Rodorubicin (Cytorhodin S, HLB 817) is a new tetraglycosidic anthracycline with interesting preclinical antitumor activity. We have performed two sequential phase I studies with the drug. In the first study Rodorubicin was administered as a single i.v. administration over* 30–360 min, *once every* 3 *weeks. The second study concerned a daily times five i.v. bolus schedule. Thirty patients entered these studies. Regardless of schedule, the dose limiting toxicity appeared to be proteinuria, which was reversible after discontinuation of the drug. Phlebitis was a cumbersome side-effect and it was initially considered to determine the MTD in the once every* 3 *weeks schedule, but finally it could be prevented by giving the drug as a bolus injection into a rapidly running infusion. Nausea and vomiting were infrequent and mild. Neither myelotoxicity nor alopecia were observed. However, even at low cumulative doses the drug was found to be cardiotoxic using both schedules of administration.*

Seven out of 12 *patients developed grade* 1–3 *cardiotoxicity, most of them above a cumulative dose of more than* 4000 μg/m^2. *These side-effects preclude a dose recommendation for phase II studies with these schedules.*

INTRODUCTION

ANTHRACYCLINES are among the most commonly used cytotoxic drugs in cancer treatment. Their widespread use, their toxicity and the frequent development of resistance of tumor cells against anthracyclines has prompted research for analogs with equal or improved antitumor activity and less toxicity.

Rodorubicin (Cytorhodin S; HLB 817) (Fig. 1) is the first compound of a group of tetraglycosidic anthracycline derivatives [1]. It is a strong intercalator acting by nucleic acid synthesis inhibition. The drug is soluble in water and normal saline.

In the usual pre-screen the drug was active against L1210 leukemia *in vitro*, and against B16 melanoma *in vivo*. In that model it was inactive against other tumors. However, in the human tumor stem cell assay *in vitro* the drug was found to be active in doxorubicin-sensitive lung cancers and in doxorubicin-resistant breast cancer, ovarian cancer, colon cancer, gastric cancer and pancreatic cancer. Besides it was active *in vivo* in the subcutaneously implanted colon and pancreatic tumors in nude mice.

In acute toxicity experiments, mice and rats showed pathological changes in kidney, spleen and heart. In subchronic toxicity studies in rats receiving 5, 16 or 50 μg/kg/day for 30 days, increases in creatinine were seen in the highest dose group. Renal changes consisted of glomerular and tubular epithelial damage, while cardiac changes were located in the myocardial cells. Subchronic toxicity in beagle dogs with a dose of 5, 16 or 50 μg/kg/day for 30 days only revealed changes in the highest dose group. Serum creatinine became increased which was related to glomerular and tubular damage at histology. The ECG showed a prolonged QT interval while at histology signs of cardiac insufficiency were noted. There was no myelosuppression.

The LD_{10} in mice was 2610 μg/m^2. Because of its different antitumor spectrum in preclinical studies as compared to doxorubicin and an expected lower rate of cardiotoxicity, Rodorubicin was selected for clinical studies. We have performed two phase I studies of Rodorubicin which are the subject of this report.

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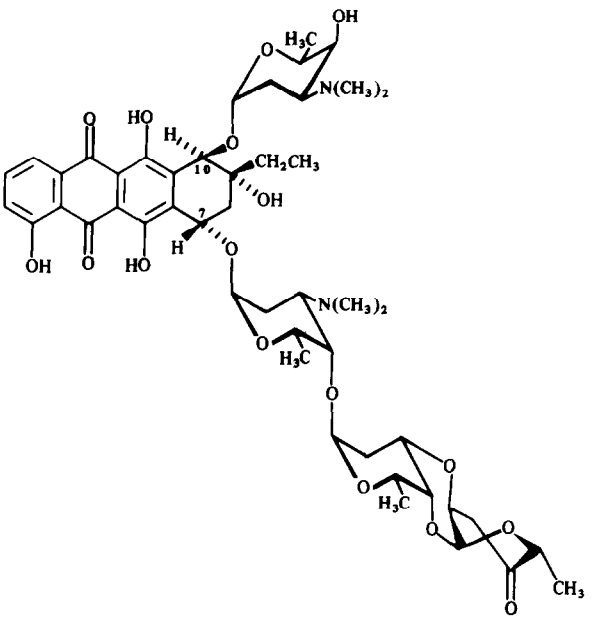

Fig. 1. Structural formula of Rodorubicin.

MATERIALS AND METHODS

Eligibility and follow-up

The study protocols were in accordance with the EORTC guidelines for phase I trials with single agents [2]. Eligibility criteria included histologically proven progressive cancer, resistant to conventional therapy, life expectancy of at least 2 months, performance score WHO ≤2, age between 18 and 75 years, no chemotherapy or radiotherapy for at least 4 weeks before entry (for mitomycin C, nitrosoureas and extensive radiotherapy: 6 weeks) and recovery from toxic effects of prior treatment, WBC ≥4 × 10^9/l, platelet count ≤100 × 10^9/l, normal bilirubin and normal renal function. All patients gave written informed consent prior to therapy.

All blood tests and urinalyses were repeated weekly while the patients were on study. Chest X-ray, gated cardiac blood pool scan (MUGA) and ECG were repeated prior to each scheduled cycle.

Drug formulation and dosage

Rodorubicin (lot No. 3) was supplied by Behringwerke AG, Marburg, F.R.G. The salt of Rodorubicin together with D-gluconic acid is a deep orange amorphous powder, well-soluble in water and in normal saline. The drug was available in vials containing 1000 μg of Rodorubicin-D-gluconate, 400 mg of mannitol and 25 mg of sodium chloride, to be reconstituted in 10 ml of water for injection. Initially the prescribed dose was further diluted with 0.9% NaCl solution to a total of 100 ml for administration as a 30-min infusion. This infusion time was chosen with the intention of trying to avoid local toxicity as bolus injections had caused local venous irritation in rabbits. When phlebitis nevertheless did occur (concomitant to proteinuria), arbitrarily chosen larger amounts of fluids, longer infusion times and finally bolus injections into rapidly running infusions were also used in an effort to prevent the observed side-effects. In aqueous solution Rodorubicin is stable over 24 h, but because of minor degradation under the influence of light, care was taken to administer the drug protected from light directly after dissolution. The starting dose was 260 μg/m^2 which represents 1/10 of the LD_{10} in mice [3]. The study on the daily times five schedule was initiated after completion of the study of the single bolus schedule. Based upon the obtained clinical data and on animal data, the starting dose for the daily times five schedule was 250 μg/m^2/day. Dose escalation was performed according to the modified Fibonacci scheme. At least three patients were studied at each dose level and there was no dose escalation within a single patient. Cycles were repeated every 3 weeks.

RESULTS

Thirty patients were entered. Patient characteristics are given in Table 1. A total of 75 evaluable cycles was administered. There were no drug-related deaths. The dose levels studied were 260, 520, 860, 1290 and 1700 μg/m^2 single administration, and 250 and 350 μg/m^2/day, days 1–5.

Leukocytopenia, thrombocytopenia and hair loss were not observed.

The *dose-limiting* side-effects of Rodorubicin were proteinuria and phlebitis. The *cumulative* side-effect was cardiotoxicity.

A significant decrease in left ventricular ejection fraction (LVEF) was noted in seven patients (Table 2), three on the day 1 q 3 weeks schedule and four on the daily times five schedule. None of the seven patients had had prior radiotherapy to the mediastinum or had received prior treatment with anthracyclines. No other risk factor could be identified. In

Table 1. Patient characteristics

No. of patients	30
Male/female	17/13
Age: median (range)	53 (34–72)
WHO performance score:	
Median	1
Range	0–2
No. of patients with:	
Previous chemotherapy	28
Previous Doxorubicin	7
Previous radiotherapy	4
Primary tumor:	
Renal cancer	10
Colon cancer	7
Soft tissue sarcoma	3
Miscellaneous	10

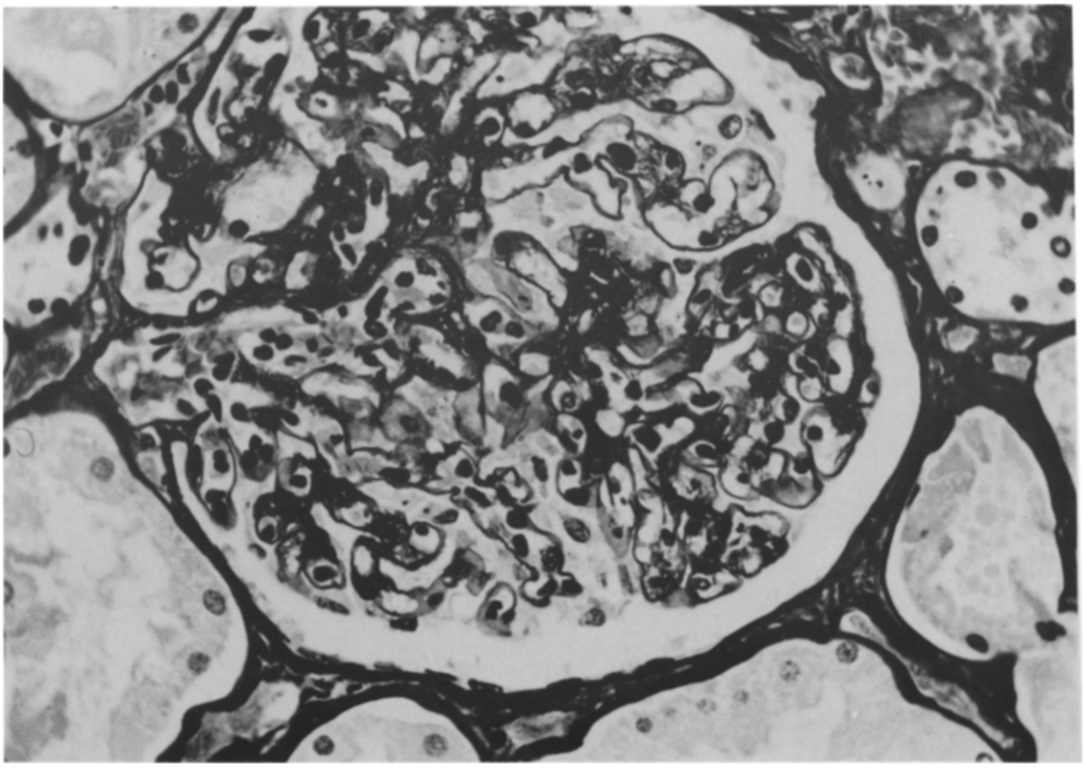

Fig. 2. Detail of glomerulus showing focal irregularities of the basal membrane (paraffin section, silver staining × 400).

Table 2. Left ventricular ejection fraction (LVEF) in relation to cumulative dose of Rodorubicin*

Cumulative dose of Rodorubicin (MCG/m²)	No. of patients evaluable at this dose level	LVEF (mean ± 2 S.E.M.)	No. of patients with abnormal LVEF (<50%)
Before treatment	30	68 ± 12	0
<1000	30	63 ± 9	0
1000–1999	24	65 ± 12	2
2000–2999	19	62 ± 9	0
3000–3999	15	55 ± 14	1
4000–4999	8	58 ± 19	1
5000–5999	7	50 ± 14	2
>6000	2	43 ± 54	1

*Normal value of LVEF: 50–70%.

three patients cardiotoxicity was symptomless, in two it was grade 2 (WHO) and in two congestive left ventricular failure developed necessitating supportive treatment. In two patients the abnormal LVEF was found after a cumulative dose of 1750 μg/m², in the others it occurred at cumulative doses of 300–6000 μg/m². In all seven patients treatment was discontinued. In four patients LVEF recovered to normal after 2–8 months, in the others long-term follow-up was impossible because of death due to malignant disease. At autopsy minute endothelial changes were found in the endocardial veins.

Proteinuria was first noted at a single bolus dose level of 860 μg/m² (Table 3). In none of the patients studied at lower dose levels was proteinuria found, even at cumulative doses up to 2860 μg/m². At dose levels of 860 and 1290 μg/m², proteinuria usually appeared after the second treatment cycle reaching a plateau level of 5–8 g/l. At a dose of 1700 μg/m², proteinuria occurred after the first cycle of treatment. By increasing the administered amount of fluid to 500 or 1000 ml and by prolonging the infusion time to 3 or 6 h the occurrence of proteinuria could be delayed until the second cycle, but it could not be prevented. Likewise Rodorubicin at a daily times five schedule did not prevent the occurrence of proteinuria. Proteinuria merely consisted of albuminuria without an increase in β_2-microglobulin. In patients in whom urinary protein loss could be monitored after discontinuation of Rodorubicin, proteinuria disappeared rapidly and completely within 3–6 weeks. In one patient a renal biopsy was taken, three patients were autopsied. Renal changes consisted of minor irregularities of the glomerular basal membrane (Fig. 2). Tubular damage was not present. Serum creatinine increases were observed in four patients, three grade 1, one grade 4. The latter patient was treated at a dose of 1700 μg/m² as a 3-h infusion. Shortly after the third cycle, at a cumulative dose of 5100 μg/m², an oliguric renal failure developed, which appeared to be reversible within 3 weeks with complete recovery of renal function.

Phlebitis at the infusion site was first noted at the 1290 μg/m² single bolus dose level, usually after 1–2 days. It was not unexpected as it was reported in the animal toxicology studies, especially in rabbits, in which animal it was seen after bolus injection and not after prolonged infusion. In the phase I studies it worsened with increasing dose and with prolonged infusion time. Some of the patients had

Table 3. Proteinuria

Dose (MCG/m²)	No. of patients	No. of cycles	(WHO grade) 0	1	2	3	4
260	3	13	13	0	0	0	0
520	3	7	6	0	0	0	0
860	3	9	2	2	5	0	0
1290 (30 min)	6*	16	3	3	10	0	0
1700 (30 min)	4	6	1	1	4	0	0
1700 (3 h)	3	6	0	2	4	0	0
1700 (6 h)	2	4	1	1	2	0	0
250 × 5 (5–30 min)	3	8	3	0	5	0	0
350 × 5 (5–30 min)	3	6	2	3	1	0	0

*Only one of six patients developed proteinuria after the first administration.

their first signs of phlebitis 7–10 days after Rodorubicin infusion. This almost excludes direct local damage as the cause. There was no recall phlebitis. Of note, one patient showed a retrograde phlebitis far into the external jugular vein up to the occiput. In five instances phlebitis caused a temporary contracture of the affected arm. Therefore, in the once every three weeks schedule phlebitis was considered dose limiting. In the daily times five study, which was performed afterward, Rodorubicin was dissolved in 10 ml of saline and administered into a rapidly running infusion in 5 min. Using this procedure no phlebitis was observed, but because of the observed incidence of cardiotoxicity this way of administration was not re-investigated in the other schedule.

Nausea and vomiting was mild to moderate and mainly present at the highest dose level studied.

In several patients fatigue was noted, which subsided after treatment was discontinued.

Tumor responses according to WHO criteria were not observed. Two patients experienced short-lasting (<4 weeks) tumor regression of less than 50%.

DISCUSSION

Based upon animal data, Rodorubicin appeared to be an interesting new anthracycline antitumor agent, particularly against colorectal tumors. Based upon animal toxicology studies, nephrotoxicity was expected, while no other significant toxicities were anticipated. In the animal model, the drug was not myelotoxic and cardiotoxicity only occured at the highest dose level tested in the subchronic toxicity investigations.

These phase I studies demonstrate that the limiting side-effects in man are cardiotoxicity and proteinuria. Cardiotoxicity appears to be related to cumulative dose, and occurs already at low cumulative dose levels of 1750–6000 $\mu g/m^2$. For this reason Rodorubicin in the schedules studied can hardly be useful for clinical application.

The proteinuria induced by Rodorubicin appears to be related to the amount of drug per administration as well as to the cumulative dose.

Proteinuria plateaus at values of 5–8 g/l and never induced a nephrotic syndrome. The fact that proteinuria was merely albuminuria suggested a glomerular disorder which was confirmed by histology. Whether the same glomerular changes were responsible for the single case of reversible renal failure that was observed remains an open question, because in that particular case no histology was obtained.

Proteinuria could be postponed but not prevented by prolonging the infusion time and increasing the infused volume, but not by giving the drug in a daily times five schedule. Proteinuria was reversible after discontinuation of treatment, even after relatively high cumulative doses. These data are in concordance with the animal data, and to our knowledge Rodorubicin is the first anthracycline that causes proteinuria in man. For doxorubicin proteinuria has been reported in animals [4] but this drug is not nephrotoxic in man.

Nausea and vomiting were mild to moderate. Myelotoxicity and hair loss were completely absent.

In conclusion, the nephrotoxicity and cardiotoxicity observed in these phase I studies constitute a major impediment to the clinical applicability of Rodorubicin and no dose recommendations for phase II studies with these schedules can be given.

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