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CLINICAL TRIAL REPORT

L.C. Pronk · W.L.J. van Putten · V. van Beurden
M. de Boer-Dennert · G. Stoter · J. Verweij

The venotonic drug hydroxyethylrutosiden does not prevent or reduce docetaxel-induced fluid retention: results of a comparative study

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Abstract *Purpose*: Fluid retention, which includes peripheral edema, ascites, pleural or pericardial effusion, or a combination of these that is sometimes associated with significant weight gain, is one of the most troublesome cumulative side effects of docetaxel. A suggestive observation from the data base available at the manufacturer (Rhone-Poulenc Rorer) was that patients who received venotonic drugs appeared to tolerate more courses of docetaxel. This prompted a comparative study to investigate whether the venotonic drug hydroxyethylrutosiden could reduce or delay docetaxel-related fluid retention. *Methods*: A total of 85 patients with metastatic breast cancer who were treated with docetaxel at a dose of 100 mg/m^2 with corticoid comedication were allocated to receive either 300 mg hydroxyethylrutosiden given orally four times daily (group A) or no hydroxyethylrutosiden (group B). The end point for analysis was the development of fluid retention of ≥grade 2. *Results*: Fluid retention of ≥grade 2 was reported in 14 of 42 patients (33%) in group A and in 15 of 43 patients (35%) in group B and occurred after a median of 4 cycles of docetaxel in both groups. Weight gain was similar in groups A and B. *Conclusion*: We conclude that hydroxyethylrutosiden does not reduce or delay the incidence and severity of docetaxel-related fluid retention.

L.C. Pronk · V. van Beurden · M. de Boer-Dennert
G. Stoter · J. Verweij
Department of Medical Oncology,
Rotterdam Cancer Institute (Daniel den Hoed Kliniek)
and University Hospital, Rotterdam, The Netherlands

W.L.J. van Putten
Department of Biostatistics,
Rotterdam Cancer Institute (Daniel den Hoed Kliniek)
and University Hospital, Rotterdam, The Netherlands

L.C. Pronk (✉)
Servicio de Oncologia Medica,
Hospital Universitario "12 de Octubre,"
Avda. Cordoba, km. 5,4, E-28041 Madrid, Spain
Tel.: 00-3491-1-390-83-49, Fax: 00-3491-1-460-33-10

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Introduction

Fluid retention, which includes peripheral edema, ascites, pleural or pericardial effusion, or a combination of these, is a troublesome and sometimes disabling side effect of docetaxel. Sometimes fluid retention is associated with a significant weight gain. The occurrence of fluid retention is related to the cumulative dose of docetaxel given, increasing in incidence at cumulative doses of ≥400 mg/m^2 [11, 16]. Recent data suggest that with corticosteroid comedication, initially intended to reduce hypersensitivity reactions, fluid retention is delayed and reduced [8]. The addition of antihistamines or 5-hydroxytryptamine$_2$ (5HT2) blockers to the co-medication schedule does not influence the occurrence in terms of severity or frequency.

A remarkable suggestion from the data base available from the manufacturer (Rhone-Poulenc Rorer) was that patients who received a so-called venotonic drug appeared to tolerate more courses of docetaxel. Since various types of venotonic drugs were given, no definitive conclusion on the value of these drugs could be given.

Hydroxyethylrutosiden (Venoruton) is a standardized mixture of semisynthetic flavonoids that primarily acts on the microvascular endothelium to reduce hyperpermeability and edema. In patients with chronic venous insufficiency or diabetes, hydroxyethylrutosiden improves microvascular perfusion and microcirculation and reduces erythrocyte aggregation. The preparation may also have a protective effect on the vascular endothelium [15]. Hydroxyethylrutosiden is a registered and widely used drug in The Netherlands. At the recommended dose of 300 mg given orally four times a day the drug does not have side effects.

In view of the observations from the data base on docetaxel and the availability of a venotonic drug

without side effects, it was considered worthwhile to perform a comparative study to investigate the value of hydroxyethylrutosiden in the prevention or reduction of docetaxel-related fluid retention.

Patients and methods

Eligibility

Patients with histologically or cytologically proven breast cancer who had started treatment with docetaxel and given oral informed consent were entered in this study. Eligibility criteria further included (1) an age of ≥ 18 years; (2) a WHO performance status of 0–2; (3) adequate hematologic (granulocytes $\geq 2.0 \times 10^9$/l), renal (serum creatinine ≤ 1.5 times the upper normal limit), and hepatic function (total serum bilirubin ≤ 1.25 times the upper normal limit, ASAT ≤ 2 times the upper normal limit); and (4) no preexisting pleural fluid, ascites, or peripheral edema except in the case of pleuritis carcinomatosa and/or peritonitis carcinomatosa.

Drug administration

Docetaxel was supplied by Rhone-Poulenc Rorer (Antony, France) as a concentrated sterile solution containing 40 mg of drug/ml in a 2-ml vial in polysorbate 80 (Tween 80). The appropriate amount of drug to be given to the patient was diluted in 5% dextrose solution (or 0.9% saline serum) such that the maximal docetaxel concentration was 1 mg/ml. The drug was given to the patient as a 1-h infusion every 3 weeks at a dose of 100 mg/m^2. All patients received comedication consisting of 8 mg dexamethasone given orally 13, 7, and 1 h before docetaxel infusion, followed by 8 mg dexamethasone given orally twice a day for 96 h after docetaxel administration. In addition, patients were allocated to (a) four oral doses of 300 mg hydroxyethylrutosiden daily until docetaxel discontinuation or the development of fluid retention of ≥ grade 2 or (b) no hydroxyethylrutosiden.

Study parameters

Prior to the start of treatment a history was taken and a physical examination, neurologic examination, and laboratory studies were performed. Laboratory studies included a complete blood count with differential white blood cell count to be performed weekly. Biochemistry determinations, including total bilirubin, alkaline phosphatase, SGOT (AST), SGPT (ALT), sodium, potassium, calcium, creatinine, total protein, and albumin, were performed every 3 weeks.

In addition to the above-mentioned tests, the existence of fluid retention was detailed by physical examination and the patient's weight was recorded. The same scales were used for each visit by the patient. During docetaxel treatment, body weight was determined and a physical examination was performed every 3 weeks to reveal potential signs of fluid retention. A computerized tomography (CT) scan of the thorax or a X-ray of the chest, if not previously indicated to follow tumor parameters, was performed every two treatment cycles. Because there is no WHO or CTC grading for edema or effusion, this was graded as follows:

1. Peripheral edema: grade 0 – no edema; grade 1 – no visual change, pitting effects; grade 2 – visual and pitting edema; grade 3 – massive edema, loss of externally visual joint anatomy; grade 4 – incapacitating edema

2. Effusion: grade 0 – no effusion; grade 1 – asymptomatic, no intervention required; grade 2 – symptomatic, exertional dyspnea and/or chest pain and/or ECG changes and/or abdominal distention, drainage may be required; grade 3 – symptomatic effusion, dyspnea at rest and/or tamponade and/or pronounced abdominal distention, drainage urgently required

Furthermore, a distinction was made between edema of the arms, edema of the legs, pleural effusion, pericardial effusion, ascites, and generalized edema.

Statistical analysis

Patients were allocated to treatment with hydroxyethylrutosiden or no treatment. For the detection of a decrease in the incidence of fluid retention from 60% to 20% with $\alpha = 0.10$ and $\beta = 0.10$, at least 80 patients had to be included in the study. The primary end point for analysis was the development of fluid retention of ≥ grade 2. Patients with preexisting pleural fluid due to pleuritis carcinomatosa were not considered evaluable for the increase in pleural fluid. However, these patients were kept in the analysis for evaluation of the development of edema at other sites. The time to treatment failure was defined as the first cycle after which fluid retention of ≥ grade 2 was observed. Some patients received diuretics because of the occurrence of mild fluid retention that had not yet reached grade 2. These patients were not considered as failures in the analysis but were censored at the start of treatment with diuretics. Patients who did not develop grade 2 fluid retention and were not treated with diuretics but stopped treatment for other reasons were censored after the last treatment cycle. The log-rank test was used to test for a difference between the two treatment groups in the probability of development of fluid retention of ≥ grade 2.

Results

A total of 85 patients were entered into this study, which was initiated in August 1994 and completed in January 1997. In all, 42 patients were allocated to treatment with hydroxyethylrutosiden (group A) and 43 patients, to the control arm (group B). The characteristics of these patients are shown in Table 1. At the start of treatment, 19 patients had pleuritis carcinomatosa. Two patients with edema of the arms and one patient with edema of the leg (all of grade 1) were included in the analyses and evaluated for the development of a higher grade of edema and/or of edema at another site.

The number of evaluable treatment cycles varied between 1 and 11 (median 4 cycles) and was similar in both groups. Overall, 40 patients did not develop fluid

Table 1 Patients' characteristics

		Treatment	
		Hydroxyethylrutosiden	Control
Number of patients		42	43
Age (years)	Median	48	50
	Range	31–68	31–73
Type/grade of fluid retention at start:			
No fluid retention		34	29
Arm	Grade 1	1	1
	Grade 2	0	0
Leg	Grade 1	0	1
	Grade 2	0	0
Pleura	Grade 1	3	7
	Grade 2	4	5

Table 2 Grade, type, and cycle of maximal fluid retention

	Treatment	
	Hydroxyethylrutosiden	Control
Grade of max. fluid retention:		
1	6	10
2	9	12
3	5	3
Type of max. fluid retention:		
Arm	6	8
Leg	9	14
Pleura	5	0
General	0	3
Cycle of fluid retention of ≥ grade 2:		
Median	4	4
Range	1–9	1–9

retention or an increase in fluid retention (in the case of preexisting edema), whereas 16 patients developed maximal fluid retention of grade 1; 21 patients, grade 2; and 8 patients, grade 3 (Table 2). The incidence of fluid retention of ≥grade 2 was similar for group A and group B (33% and 35%, respectively). In most patients, fluid retention was located in the legs or arms. The type of fluid retention was similar in both groups. The median number of cycles received before fluid retention of ≥grade 2 developed ($n = 29$) was 4 (range 1–9). Grade 2 fluid retention occurred late (after cycle 6) in only 3 of the 11 patients who received more than 6 cycles of docetaxel and who remained at risk for the development of fluid retention. Figure 1 shows the actuarial probability of the development of fluid retention of ≥grade 2 in the two groups. The actuarial probability after six cycles was approximately 45% and was similar in both groups (log-rank test, $P > 0.20$).

Only 45 patients experienced a consistent increase in weight after at least one cycle relative to pretreatment values, with the median maximal increase in weight being 5.5% (range 0.3–32%). This maximal increase was observed after a median of four cycles. On the other hand, most of the patients showed a (sometimes minor) decrease in weight after at least one cycle relative to pretreatment values, with the median decrease being 3.3%.

The most important reason for termination of the study was discontinuation of treatment with docetaxel due to progressive disease and/or toxicity in 25 patients (60%) in group A and 22 patients (51%) in group B. Only two patients refused to take hydroxyethylrutosiden after one and two treatment cycles, respectively. In all, 7 patients (17%) in group A and 15 patients (35%) in group B were given diuretics given because of development of fluid retention. One patient in group A and four patients in group B were given diuretics even though there was no fluid retention of ≥ grade 2. In six patients in group A and group B the study was discontinued because of toxicity alone, which consisted of edema in five patients in each group.

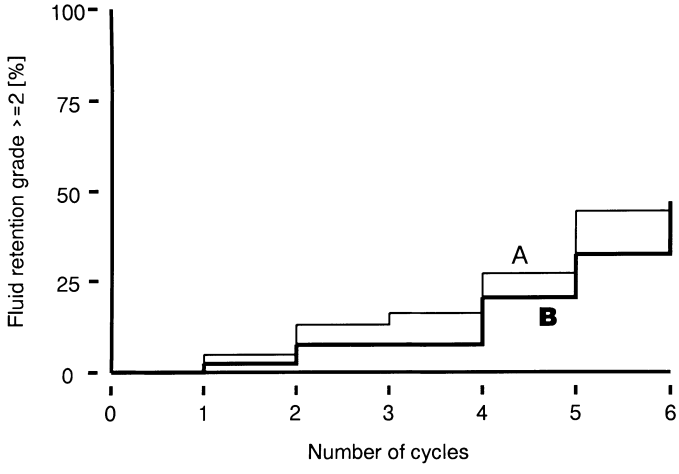

Fig. 1 Actuarial probability of the development of fluid retention of ≥ grade 2 in groups A and B

Discussion

Fluid retention is one of the most troublesome side effects of docetaxel. It appears to be related to the cumulative dose, increasing in incidence at cumulative doses of ≥400 mg/m^2 [1, 2]. The incidence of fluid retention reported in various phase II studies ranges from 9% to 89% [2, 3, 5–8, 12–14]. The EORTC Clinical Screening Group investigated whether prophylactic premedication that consisted of 5 mg dexchlorpheniramide and 50 mg ranitidine given i.v. 30 min before docetaxel administration plus 130 mg prednisolone given orally 12 and 6 h before chemotherapy could reduce the incidence and severity of fluid retention observed in other studies [6]. Among 37 evaluable patients, fluid retention occurred in 89.2% and was moderate in 32.4% and severe in 10.8%. Fluid retention was a reason for study discontinuation in 43.2% of the patients. The median cumulative dose received until the onset of fluid retention was 301 mg/m^2, and that received until treatment discontinuation due to fluid retention was 698 mg/m^2. The investigators concluded that the above-mentioned premedication failed to reduce or delay the incidence of fluid retention.

In a phase II study of the EORTC Breast Cancer Study Group, docetaxel was given at a dose of 50 mg/m^2 on days 1 and 8 every 3 weeks, and patients were randomized to receive a prophylactic oral antihistamine with versus without methylprednisolone [8]. In the patients who received steroids the incidence of edema, pleural and pericardial effusion, and weight gain was lower than in the patients who were not treated with steroids. Although corticosteroid premedication appeared to decrease the incidence of fluid retention, it remained a frequent reason for treatment discontinuation. Presently, corticosteroid co-medication, consisting of 8 mg dexamethasone given orally twice a day starting 1 day before docetaxel infusion and continued for 96 h after docetaxel administration, is routinely applied.

A remarkable suggestion from the data base available from the manufacturer (Rhone-Poulenc Rorer) was that patients who received a so-called venotonic drug could tolerate more courses of docetaxel. This prompted a comparative study on the venotonic drug hydroxyethylrutosiden to assess the value of this drug in the prevention of docetaxel-related fluid retention.

Hydroxyethylrutosiden (a benzopyrone derivative) is a standardized mixture of semisynthetic flavonoids, mainly mono-, di-, tri-, and tetrahydroxyethylrutosides, that primarily acts on the microvascular endothelium to reduce hyperpermeability and edema. Furthermore, it improves the microvascular perfusion and microcirculation and reduces erythrocyte and platelet aggregation while preserving erythrocyte deformability [15]. Although a variety of actions of hydroxyethylrutosiden have been identified, the predominant mechanism of its clinical effects has yet to be determined.

The benzopyrones have been studied in the treatment of lymphedema of the arms and legs [1, 4, 9]. In these studies, patients with postmastectomy lymphedema of the arm and/or lymphedema of the leg of various causes were randomized to treatment with benzopyrones or with placebo. The conclusion of these studies was that treatment with benzopyrones resulted in a slow reduction in lymphedema of the extremities and an improvement in general well-being.

To date, no comparative study has been performed to assess the role of hydroxyethylrutosiden in the prevention and/or reduction of docetaxel-related fluid retention. In the present study, 85 patients with metastatic breast cancer who were treated with docetaxel and corticosteriod comedication were entered. None of the patients received hormone treatment concomitantly. Patients were allocated to receive four oral doses of 300 mg hydroxyethylrutosiden daily or no hydroxyethylrutosiden. The primary end point for analysis was the development of fluid retention of ≥ grade 2. In all, 42 patients were allocated to treatment with hydroxyethylrutosiden (group A) and 43 patients were allocated to the control arm (group B). A total of 40 patients did not develop fluid retention or an increase in fluid retention. In 14 patients (33%) in group A and 15 patients (35%) in group B, fluid retention of ≥ grade 2 occurred that was located in the extremities in most cases. In these patients, other causes of fluid retention such as deep venous thrombosis and/or cardiac disease were excluded. Furthermore, iatrogenic causes (for example, the use of beta-blockers) were explored. In both groups, fluid retention of ≥ grade 2 was documented after a median of four cycles of docetaxel treatment.

Of our patients, 45 showed weight gain that ranged from 0.3% to 31.8%, with the median being 5.5%. The most frequent reason to stop the study was discontinuation of treatment with docetaxel due to progressive disease and/or docetaxel-related toxicity. Diuretics were started more often in group B than in group A. In one patient in group A and four patients in group B, diuretics were started even though no fluid retention of ≥ grade 2 was scored. As the decision to start diuretics in the case of mild retention could have been influenced by the knowledge of whether the patient was receiving hydroxyethylrutosiden in this open, non-placebo-controlled comparative study, we censored these five patients in our analysis with the time to objective grade 2 fluid retention as the primary end point.

We conclude that hydroxyethylrutosiden does not reduce or delay the incidence and severity of docetaxel-related fluid retention. This is in concordance with the results published by Riva et al. [10], who showed that the addition of the venotonic drug diosmine to corticosteriod premedication did not ameliorate the efficacy of corticosteroids alone. In view of the observation that 45% of our patients developed fluid retention of ≥ grade 2 after receiving six cycles despite corticosteroid comedication, there is a need for further studies on the prevention of this troublesome side effect.

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