

The pathophysiological mechanism of fluid retention in advanced cancer patients treated with docetaxel, but not receiving corticosteroid comedication

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Aims Fluid retention is a phenomenon associated with taxoids. The principal objective of this study was to investigate the pathophysiological mechanism of docetaxel-induced fluid retention in advanced cancer patients.

Methods Docetaxel was administered as a 1 h intravenous infusion every 3 weeks, for at least 4–6 consecutive cycles, to patients with advanced breast ($n=21$) or ovarian ($n=3$) carcinoma, who had received previous chemotherapy, 21 for advanced disease. Phase II clinical trials have shown that 5 day corticosteroid comedication, starting 1 day before docetaxel infusion, significantly reduces the incidence and severity of fluid retention. This prophylactic corticosteroid regimen is currently recommended for patients receiving docetaxel but was not permitted in this study because of its possible interference with the underlying pathophysiology of the fluid retention.

Results Fluid retention occurred in 21 of the 24 patients but was mainly mild to moderate, with only five patients experiencing severe fluid retention. Eighteen patients received symptomatic flavonoid treatment, commonly prescribed after the last cycle. Specific investigations for fluid retention confirmed a relationship between cumulative docetaxel dose and development of fluid retention. Capillary filtration test analysis showed a two-step process for fluid retention generation, with progressive congestion of the interstitial space by proteins and water starting between the second and the fourth cycle, followed by insufficient lymphatic drainage.

Conclusions A vascular protector such as micronized diosmine hesperidine with recommended corticosteroid premedication and benzopyrones may be useful in preventing and treating docetaxel-induced fluid retention.

Keywords: fluid retention, docetaxel, advanced cancer, corticosteroid, premedication

Introduction

Docetaxel belongs to a new class of antineoplastic agents, known as taxoids. At the recommended dosage of 100 mg/m² given as a 1 h infusion every 3 weeks, docetaxel monotherapy has produced impressive response rates in a variety of advanced malignancies, particularly metastatic breast cancer [1] and non-small-cell lung cancer [2]. Significant activity has also been seen in ovarian cancer, with data indicating a level of activity that is at least as high as that of paclitaxel at an equivalent stage of development [3].

Fluid retention is an adverse event associated with the taxoid group of drugs and this can occasionally lead to discontinuation of treatment [1–3]. The development of fluid retention appears to be related to the cumulative dose of docetaxel administered and occurs typically after 3–5 cycles of therapy. However, in phase II clinical trials, 5 day treatment with corticosteroids, starting 1 day before docetaxel administration, reduced the incidence of severe cases of fluid retention from 20% to 6%, reduced the number of

patients discontinuing treatment because of this adverse event from 32% to 3% and increased the median cumulative dose to onset of moderate or severe fluid retention from 490 to 746 mg/m² [4]. As a result, this prophylactic corticosteroid regimen is currently recommended for docetaxel patients in whom corticosteroid use is not contraindicated.

Docetaxel-induced fluid retention is not sensitive to the recumbent position, is not accompanied by episodes of dehydration, oliguria or hypotension, and is slowly reversible after cessation of docetaxel treatment. Patients typically present with peripheral oedema, which starts at the lower extremities (ankles) but can become generalized. The symptomatology is indicative of a capillary hyperpermeability syndrome. Investigators have used the capillary filtration test [5–7] and microcirculation tests [8, 9] to examine this hypothesis in 12 patients with ovarian cancer. Preliminary results showed a disturbance of the capillary permeability, with a secondary effect on lymphatic resorption. In addition, blood tests performed during docetaxel infusion showed a significant increase in circulating lymphokine-activated killer (LAK) cells, which may be involved in the development of docetaxel-induced fluid retention.

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Given these observations, we undertook a study to define the pathophysiology of fluid retention in patients receiving a 1 h infusion of docetaxel every 3 weeks for advanced breast or ovarian carcinoma. We also aimed to characterize further the safety profile and to determine the antitumour effect of docetaxel. Prophylactic corticosteroid comedication was not permitted because of its potential interference with the pathophysiology of docetaxel-induced fluid retention.

Methods

This multicentre, open-label, non-randomized study was designed to examine the pathophysiology of fluid retention in advanced cancer patients treated with a 1 h intravenous infusion of docetaxel 100 mg/m² every 3 weeks for at least 4–6 consecutive cycles. Each cycle was given at the same dose, although dose modification was permitted for myelosuppression, hypersensitivity reactions, cutaneous reactions or toxicities of grade 3 or more, excluding alopecia and anaemia. Doses reduced for toxicity could not be re-escalated to the starting level. Patients were withdrawn if progressive disease or unacceptable toxicity was evident, at the patient's request, or if the investigator believed withdrawal to be in the patient's best interest. Patients were investigated prospectively on a regular basis and observed for 1 month after the last docetaxel infusion, then every 3 months, to document late side-effects and to follow continuing toxicities to complete recovery. The study was conducted in accordance with the Declaration of Helsinki (Hong Kong amendment). Ethics committee approval was obtained before commencement and written informed consent was obtained from patients before each inclusion.

The following concomitant therapies were not permitted: diuretics or calcium antagonists; other experimental, investigational drugs or anticancer treatments; colony-stimulating factors such as granulocyte colony-stimulating factor, unless indicated medically; radiotherapy, unless for local control of bone pain; and prophylactic anti-infective, antiemetic or antiallergic (antihistamines/glucocorticosteroids) medications. The use of prophylactic corticosteroid medication was not permitted because of possible interaction with the underlying pathophysiology of docetaxel-induced fluid retention. Flavonoid therapy could be used for severe fluid retention that was poorly tolerated, but no other treatment for fluid retention was allowed. Curative antiemetics (except steroids) and antiallergic measures were permitted, but other toxic effects were managed symptomatically if possible.

Inclusion and exclusion criteria

Eligible patients had histologically or cytologically confirmed advanced breast or ovarian carcinoma and had failed first- or second-line chemotherapy. Patients were required to have been off their previous antitumour therapy for at least 4 weeks, or 6 weeks for mitomycin C, nitrosurea or extensive radiotherapy ($\geq 30\%$ of bone marrow). Patients had to be 18–70 years of age, with normal blood counts, liver and renal function tests, a maximum World Health Organization (WHO) performance status of 2, and a life expectancy of at least 12 weeks.

Specific conditions for ineligibility were pregnancy,

lactation and child-bearing potential; concurrent serious medical illness; previous malignancy; evidence of effusions; signs of localized or generalized oedema; inferior limb ulcers from trophic, venous or arterial aetiology; and previous therapy with paclitaxel or docetaxel.

Study assessments

Regular safety assessments were performed to identify clinical, biological and laboratory abnormalities, haematological toxicities, febrile neutropenia, infections and non-haematological toxicities.

Several specific investigations were performed for fluid retention, which was defined as at least one of oedema or peripheral oedema, effusion (pleural effusion, ascites, pericardial effusion) and weight gain. A weight assessment was performed by the patient twice a day at the same times and under similar conditions. Clinical measurements of ankles, calves, thighs, hips, breast and waist were performed every 3 weeks. A capillary filtration test, using technetium-99m-labelled albumin was performed to determine a pathophysiological model of docetaxel-induced fluid retention and to test the ability of flavonoids to improve symptomatology. This test is used routinely to confirm idiopathic cyclic oedema or microangiopathy in diabetes, shown by pathological retention of albumin in the upper limbs after the release of a tourniquet. Patients with oedema related to abnormal lymphatic function also have irregular oscillations after tourniquet removal, studied by Fast Fourier Transform analysis [5, 6, 10]. Normal values for albumin retention and lymphatic oscillations are $< 8\%$ and $< 10\%$, respectively. The signal usually disappears towards the 32nd harmonic, falling to values 10^{-6} times smaller than the fundamental value. During oedema (like idiopathic orthostatic oedema), the amplitudes measured are only 10^{-2} times lower than the fundamental value, for frequencies of 2 mHz. This one is corresponding to temporal phenomena of around 1 min and therefore slow. In addition to double labelling values intended to verify the reality of these results, they may be compared to the modern conception of the role of the lymphatic pumps: experimentally, numerous data confirm the rhythmic response of the initial lymphatic system, when saturation of lymphatic pumping by the lymphatic clusters occurs. The phenomenon of saturation-desaturation, with the same frequency only in this kind of oedema, has been compared by Taylor [11] to a 'peripheral lymphatic heart'. Leg volumetry was performed to quantify fluid retention in the lower limbs, percutaneous capillaroscopy was used to study capillary structure in the percutaneous and pericapillary areas and flux laser Doppler was carried out to quantify cutaneous microvascular flow and its fluctuation.

The median duration of fluid retention was calculated from the first occurrence to the last stop date and, to assess reversibility, from the date of the last infusion to the stop date. Patients with ongoing fluid retention were treated as censored observations, in which the calculated stop date was the date of the last recorded ongoing fluid retention, the date of death or the date of last contact. Calculations were performed using the Kaplan-Meier method.

Efficacy assessments were performed for patients with measurable or evaluable lesions at entry who had received

at least two cycles of treatment. Disease progression before the start of the second cycle was classified as treatment failure. Patients were non-evaluable if they were removed from the study in the 3 weeks after the first infusion. Measurable or evaluable disease was not mandatory. Tumour size and overall response to therapy were classified according to WHO criteria.

Statistical analysis

A minimum of 20 patients were to be included in the study, to enable evaluation of at least 20 patients who had received 4–6 cycles of docetaxel. The statistical analysis of patient characteristics was descriptive and performed on the intent-to-treat population. Descriptive statistics were also used to summarize efficacy and safety data. All patients who started at least one docetaxel infusion were analysed for safety, and those with at least one blood count between days 6 and 15 were considered for haematological analysis. Adverse events were analysed during treatment and follow-up. National Cancer Institute Treatment Criteria were used to grade and classify adverse events wherever possible, although a specific three-point severity-grading system was used for fluid retention, to standardize investigators' assessments (Table 1).

Additional statistical tests were used to study the relationship between cumulative dose and the results of the capillary filtration test. The first hypothesis was that albumin retention levels and lymphatic fluctuations increase as cumulative dose increases. Cycles C0, C2, C4 and C6 were used to create groups for cumulative dose, and the Kruskal-Wallis test was used to determine whether the distribution of labelled albumin level and lymphatic fluctuation values was similar across these groups, with each value being assigned a rank score. A second hypothesis was that albumin retention level and lymphatic fluctuation values increase from baseline to C2. A paired, one-sided *t*-test was performed on the change from baseline to C2 for each of these parameters.

Results

Baseline characteristics

Of the 24 women in this study, 21 had adenocarcinoma of the breast and three had ovarian adenocarcinoma. At study entry, one patient in the breast carcinoma group had a locally advanced adenocarcinoma; the remaining 20 (95%) had metastatic disease, 10 with involvement of two organs and three with involvement of three organs. Liver (15/21), bone (8/21), lymph nodes (6/21) and lung (2/21) were the organs most frequently affected. The median age was 50 years (range 31–67) in the breast carcinoma group and 55 (range 49–56) in the ovarian carcinoma group. Half of the patients were postmenopausal. The median performance status at baseline was 1 (range 0–2).

Previous anticancer treatment included surgery ($n=23$), radiotherapy ($n=21$), hormonal therapy ($n=16$) and chemotherapy ($n=24$). One patient had received neoadjuvant and adjuvant chemotherapy only, two patients had received adjuvant chemotherapy only and 21 patients had received chemotherapy for advanced disease; hence a total of three patients received docetaxel as first-line chemotherapy for advanced disease. In the breast-carcinoma group, the median number of previous chemotherapy regimens was 2 (range 1–4), the median number of drugs received was 4 (range 1–8) and the median time between last chemotherapy and first infusion was 10.5 months (range 1–40.8). Previous medical histories or concomitant medical conditions did not prevent inclusion in safety analyses.

Treatment administration

All 24 patients received at least two cycles of docetaxel, and 22 patients received at least four cycles. A total of 127 cycles were administered: 126 at 100 mg/m² and one at 75 mg/m². The median actual dose over all cycles was 98.4 mg/m².

Table 1 Fluid retention grading.

Oedema	Severity grading	Effusion
<ul style="list-style-type: none"> ● Asymptomatic and/or ● Very well tolerated and/or ● Dependent in evening only 	MILD 1	<ul style="list-style-type: none"> ● Asymptomatic ● No intervention required
<ul style="list-style-type: none"> ● Moderate functional impairment and/or ● Pronounced and well tolerated and/or ● Dependent throughout day 	MODERATE 2	<ul style="list-style-type: none"> ● Symptomatic effusion, drainage may be required <ul style="list-style-type: none"> – exertional dyspnoea and/or – chest pain and/or ● Electrocardiogram changes and/or ● Abdominal distension
<ul style="list-style-type: none"> ● Significant impairment of function and/or ● Pronounced and not well tolerated and/or ● Generalized anasarca 	SEVERE 3	<ul style="list-style-type: none"> ● Symptomatic effusion, drainage urgently required <ul style="list-style-type: none"> – dyspnoea at rest and/or – tamponade and/or – pronounced abdominal distension

(range 94.1–103.3), and the median cumulative dose was 535.8 mg/m² (range 188.9–808.7). The median dose intensity was 32.5 mg/m² per week (range 30.2–33.5), and the median relative dose intensity was 0.98 (range 0.90–1.01).

Efficacy

Patients were considered evaluable for response to docetaxel if they had received at least two courses of treatment, had been followed for response and presented with target lesions. Seventeen of the 24 patients had measurable disease (uni- or bidimensionally) at entry and were therefore evaluable for tumour response by objective criteria; of these, eight (47%) had partial response as their best response to docetaxel treatment. The remaining seven patients had non-evaluable disease and were therefore non-evaluable for tumour response by objective criteria.

Safety

Of the 24 patients who received at least one cycle of study drug administration, five were withdrawn because of disease progression, eight withdrew because of toxicity and 11 completed their treatment according to the protocol. No deaths occurred during the study or within 30 days of the last infusion. Seven patients experienced serious adverse events, namely infection ($n=4$), febrile neutropenia ($n=1$), thoracic pain ($n=1$) and dyspnoea ($n=1$).

With regard to haematological toxicities, grade 1 or 2 anaemia and grade 3 or 4 leucopenia and neutropenia were frequent, whereas thrombocytopenia occurred sporadically. Despite the high incidence of grade 4 neutropaenia (92%), only one patient experienced febrile neutropaenia (at C6); this patient was treated with oral antibiotics and did not require hospitalization. Infection occurred in six patients; grade 2 infection with grade 4 neutropaenia was observed in five of six episodes. Acute non-haematological toxicities possibly or probably related to study medication were generally well tolerated. Among the chronic non-haematological toxicities possibly or probably related to study medication, neurotoxicity (sensitivomotor neuropathy confirmed by electromyogram) in association with fluid retention resulted in the withdrawal from study of two patients.

Because corticosteroid comedication was not permitted, fluid retention occurred in all 21 breast cancer patients but not in the ovarian carcinoma group. The most frequent

clinical appearance of the fluid retention was a soft pitting oedema, beginning at the ankles and extending progressively to the lower limbs. In its more severe form the oedema extended to the upper extremities or to the face, and was associated with functional disturbances, such as difficulty in walking or stiffness of the joints. At a later stage the oedema generally became hard, with an elastic appearance, suggesting lymphatic involvement. Fluid retention was associated with pleural or pericardial effusion in nine of the 21 patients. In some cases, fluid retention was associated with other toxicities, such as skin reactions, nail disorders, rhinitis, lacrimation disorders or neurological disorders.

The median cumulative dose to onset of fluid retention was 301 mg/m² (range 95–710). The severity grades at onset were mild for 19 patients and moderate for two patients. The most severe grades recorded during the study were mild for five patients, moderate for 11 patients and severe for five patients. Eight patients discontinued the study because of fluid retention. The cumulative dose to treatment discontinuation ranged from 395 to 505 mg/m². Eighteen patients received symptomatic treatment with flavonoids (diosmine 2 g/day), which were prescribed most often after the last cycle, and continued until complete resolution. The median duration of fluid retention from first start to last stop was 19.0 weeks (range 6.0–27.7), and the median reversibility of fluid retention from last infusion to stop date was 12.0 weeks (range 3.0–18.0). These results reflect the fact that prophylactic corticosteroid comedication was not permitted in this study.

Weight gain was not a sensitive sign for fluid retention; weight changed by <5% from baseline for 14 of the 21 patients with fluid retention, and five patients with a weight gain of >10% had fluid retention that was mild ($n=1$), moderate ($n=3$) or severe ($n=1$). The effect of tumour response on weight cannot be excluded. Clinical measurements revealed mean increases of 6.5 cm in the waist, 2.36 cm in the right ankle, 2.57 cm in the left ankle, 1 cm in the right and left calves and >1 cm in the right and left thighs, and confirmed that the oedema tended to be localized in the lower limbs and waist.

Capillary filtration test results are presented in Table 2. Albumin retention levels increased steadily from baseline to C6 for most patients. Lymphatic fluctuations also showed a general increase over time, but this effect occurred later than the increase in albumin retention, as shown by the results of the paired one-sided *t*-test, which revealed that, after two

Table 2 Results of capillary filtration and Kruskal-Wallis tests, by cycle.

Cycle	Albumin retention				Lymphatic fluctuation			
	Capillary filtration test		Wilcoxon scores		Capillary filtration test		Wilcoxon scores	
	< 8% (normal)	≥ 8% (abnormal)	Actual	Expected	< 1% (normal)	≥ 1% (abnormal)	Actual	Expected
0 ($n=24$)	21	3	511.0	960.0	21	3	742.5	960.0
2 ($n=23$)	8	15	949.0	920.0	16	7	796.5	920.0
4 ($n=20$)	3	17	1113.5	800.0	8	12	1039.5	800.0
6 ($n=12$)	4	8	586.5	480.0	4	8	581.5	480.0
			χ^2 (3df) $P<0.0001$				χ^2 (3df) $P=0.007$	

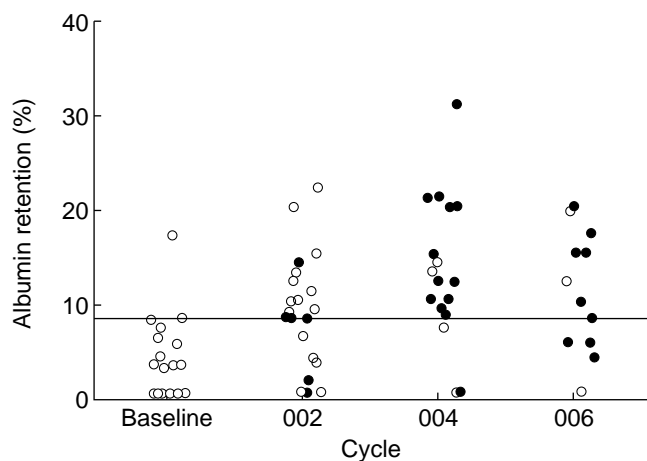


Figure 1 Capillary filtration test: albumin retention by patient and cycle, including onset of fluid retention. Patients without fluid retention, ○; patients after onset of fluid retention, ●.

cycles, the increase from baseline was statistically significant for mean albumin retention level ($P < 0.001$), but not for lymphatic fluctuations. After four cycles, however, capillary permeability and lymphatic fluctuations were clearly disturbed.

The Kruskal-Wallis test indicated that both albumin retention levels and lymphatic fluctuations tended to be related to cycle (i.e. to cumulative dose; Table 2). A clear illustration of the relationship between cumulative dose of docetaxel received and albumin retention level increase is given in Figure 1. In general, the change in albumin retention levels (C2) preceded the clinical expression of fluid retention (C4).

Patients evaluated at follow-up showed a recovery from abnormal albumin retention levels and lymphatic oscillations that tended to correspond with recovery from clinical fluid retention. Within 2 months of the last infusion, six of 14 patients evaluated had abnormal albumin retention levels (overall mean 8.6%), and five had abnormal lymphatic oscillations (overall mean 0.75%). Within 4 months of the last infusion, two out of seven patients evaluated had abnormal albumin retention levels (overall mean 6.8%), and one had abnormal lymphatic oscillations (overall mean 0.47%). The mechanism of action of the flavonoid, micronized diosmine

Table 3 Results of microcirculation tests.

Test	Change from baseline by cycle			
	Baseline (n = 17)	2 (n = 11)	4 (n = 13)	6 (n = 7)
Right leg volumetry (ml)				
Mean	2392.94	35.00	171.15	355.00
s.e.mean	55.24	19.02	48.00	108.18
Left leg volumetry (ml)				
Mean	2412.06	35.91	162.31	373.57
s.e.mean	55.09	16.72	44.92	112.59
Periungual score				
Mean	1.88	0.27	0.77	1.29
s.e.mean	0.21	0.14	0.23	0.47
Laser Doppler ($t_{\frac{1}{2}}$ -seconds)				
Mean	3.91	0.03	0.29	2.93
s.e.mean	0.61	1.25	1.34	2.17

$t_{\frac{1}{2}}$, half-life.

hesperidine, may have had a positive impact on the normalization of capillary filtration test results. However, no definite conclusion can be drawn on the impact of flavonoids on the duration of fluid retention because micronized diosmine hesperidine was not administered from the onset of the fluid retention, the numbers of patients involved were too small and comparative data were unavailable.

Microcirculation test results are presented in Table 3. The mean leg volumetry (right and left) increased from baseline by more than 100 ml at C4, in association with the clinical expression of fluid retention development, and by more than 300 ml at C6. Periungual capillaroscopic visualization of the pericapillary oedema revealed a cumulative dose effect after C4 and C6, concomitant with the clinical expression of fluid retention (Figure 2). Laser Doppler test fluctuations confirmed the increase in cutaneous capillary flow, in relation to the number of cycles received. At C4, approximately half of the patients with increased laser Doppler test results had developed clinical fluid retention.

No cardiovascular abnormalities, assessed by clinical evaluation and electrocardiogram, were observed during this

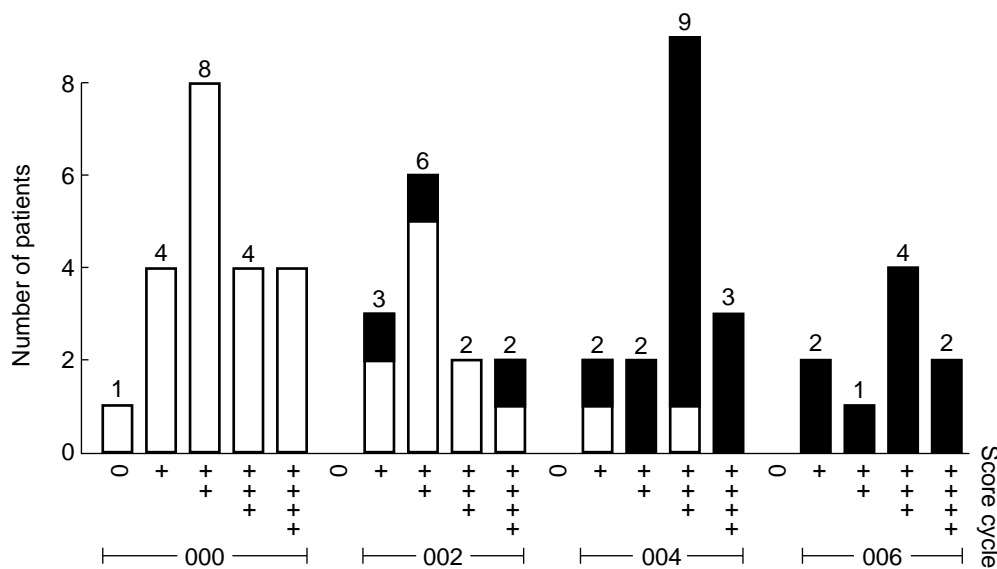


Figure 2 Periungual score from periungual capillaroscopy test, by cycle. Patients without fluid retention, □; patients after onset of fluid retention, ■.

study, and liver function tests revealed no significant abnormalities in hepatic function. In addition, no significant abnormalities in biological parameters (total protein, haematocrit, tubular markers of renal function, plasmatic renin activity and plasmatic aldosterone) were observed. Because most of the total protein and haematocrit values were normal at baseline and remained normal throughout the study, the development of fluid retention does not appear to be associated with haemoconcentration. Circulating natural-killer/LAK cells increased significantly just after infusion of docetaxel, without any cumulative effect during the study, and no correlation was seen between development of fluid retention and lymphokine stimulation.

Discussion

The results of this study have confirmed the relationship between cumulative dose and the development of a reversible fluid retention syndrome in advanced cancer patients treated with docetaxel. The most frequent clinical appearance of the fluid retention was a peripheral soft pitting oedema of the lower extremities that progressed to a lymphoedema at a later stage. On the basis of capillary filtration test findings, a two-stage pathophysiological mechanism for docetaxel-induced generation of fluid retention can be proposed.

The first indication of onset of fluid retention is the excessive transcapillary filtration of proteins, which occurs specifically through small pores [11]. This phenomenon was confirmed by the kinetics of technetium-labelled albumin, which show abnormal retention after the removal of a tourniquet. By contrast, although the lymphatic system is already required to drain excess protein, in general no signs of failure of this function are seen. At this point therefore the primary toxic effect is on the capillary endothelium. Congestion of the interstitial space by proteins, and subsequently by water, develops between the second and fourth cycles. Capillary hyperpermeability is unequivocal and signs of lymphatic failure appear, but results are widely scattered, suggesting a large interindividual variation in draining capacity. Clinical fluid retention appears mainly at this stage and can be sufficiently severe to require withdrawal of treatment, if no corticosteroid comedication is used. Hence, in accordance with microcirculation test results, this congestion of the interstitial space is the first event in the process leading to fluid retention [12]. The mechanism is completed by an insufficiency in lymphatic drainage occurring mainly after the fifth cycle and is marked by clearly pathological lymphatic fluctuations and fluid retention that may be more or less severe but is in any case clinically evident. All the conditions necessary for the oedema to evolve by itself are now present.

The underlying rationale for studying the pathophysiology of the fluid retention syndrome is to identify therapeutic strategies that will prevent or counteract the condition, in addition to the currently recommended prophylactic corticosteroid treatment. This study has provided an encouraging indication of the positive effects of high doses of the flavonoid vascular membrane protector micronized diosmine hesperidine on fluid retention, despite the small number of patients involved (18/21). Consequently, and in view of the observation that capillary hyperpermeability starts at an early

stage, one might propose routine treatment with micronized diosmine-hesperidine, at an initial dose of 2 g day⁻¹, starting at the beginning of docetaxel therapy, and increasing to 3 g day⁻¹ around the fourth cycle if necessary. In addition, the coumarin-derived benzopyrones may be useful in minimizing the build-up of proteins, particularly those with a high molecular weight, because they 'break' proteins, facilitating their elimination by the lymphatic route from the second cycle onwards, as do the flavonoids [13, 14].

A vascular protector such as diosmine with the recommended corticosteroid comedication and benzopyrones may be useful in both preventing and treating fluid retention induced by docetaxel. Further studies involving larger numbers of patients are required for a thorough assessment of this hypothesis.

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