MODULATION OF DOCETAXEL TREATMENT

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MODULATION OF DOCETAXEL TREATMENT

DOCETAXEL; COMBINATIE-CHEMOTHERAPIE EN PREVENTIE VAN BIJWERKINGEN

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Ter nagedachtenis aan Paul en mijn ouders

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INTRODUCTION

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The taxanes are a new class of drugs that exert antitumor activity through a unique mechanism. As early as in the late 1960s paclitaxel, extracted from the bark of the Pacific Yew Taxus Brevifolia, was the first compound with a taxene ring that exhibited antitumor activity (1,2). Because of the difficulties in drug isolation, extraction and formulation, the development of this antitumor agent has been relatively slow. In 1986 docetaxel, the second drug in this new class of compounds, was developed. Docetaxel is synthesized from 10-deacetyl baccatin III, a noncytotoxic precursor extracted from the European Yew Taxus Baccata (3).

Taxanes promote the polymerization of tubulin into stable microtubules and inhibit microtubule depolymerization. This leads to a disruption of the equilibrium within the microtubule system and ultimately leads to cell death (4-6). The activity of docetaxel was studied in many murine tumor models that showed that docetaxel was active against subcutaneous B16 melanoma (7), MX-1 mammary cancer (8), C38 colon carcinoma, CX-1 colon carcinoma, LX-1 lung carcinoma (9), PO3 pancreatic carcinoma, SK MEL-2 melanoma and OVCAR-3, HOC 8, HOC 10 and HOC 22 ovarian carcinomas (8,10).

In phase I studies on single agent docetaxel responses were reported in various tumor types such as breast cancer, ovarian cancer, adenocarcinoma of unknown primary, pancreatic cancer, small cell and non-small cell lung cancer (11-16). The major dose limiting toxicity was an early-onset, short-lasting, dose-dependent, schedule-independent and non-cumulative neutropenia. Other side effects were generally mild and consisted of alopecia, nausea, vomiting, diarrhea, mucositis, neurotoxicity, infrequent hypersensitivity reactions, fluid retention and skin- and nailtoxicity. For phase II studies the recommended dose and schedule was 100 mg/m^2 given as a 1-hour infusion every 3 weeks.

Phase II studies on docetaxel among others showed activity in breast cancer (17-21), non-small cell lung cancer (22-24), head and neck cancer (25), gastric cancer (26), melanoma (27), soft tissue sarcoma (28), and

pancreatic cancer (29).

In view of the fact that docetaxel is effective in a variety of solid tumors, it was considered important to study the combination of the drug with other potent antitumor agents. This thesis includes phase I studies on the combination of docetaxel with cisplatin and ifosfamide, respectively. Fluid retention and neurotoxicity, occurring in relation to the cumulative docetaxel dose (30-32), are besides activity important features. At high cumulative doses of docetaxel these side effects may become severe and disabling and lead to treatment discontinuation. It is important to try to alleviate these side effects in view of the single agent use but also in view of expected increased toxicity in case of combination chemotherapy. Therefore we performed a prospective study on the incidence of neurotoxicity induced by the combination of docetaxel and cisplatin, two potentially neurotoxic drugs.

Despite corticosteroid comedication fluid retention still occurs. In view of case reports suggesting amelioration of this side effect by venotonic drugs, we performed a prospective study on the venotonic drug hydroxyethylrutosiden in patients treated with docetaxel.

The neurotoxicity induced by docetaxel was previously reported in studies where corticosteroid comedication was not given routinely. Although introduced to reduce docetaxel-related fluid retention, it was yet unknown if corticosteroids also had an effect on neurotoxicity. This was assessed prospectively in the last chapter.

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DOCETAXEL (TAXOTERE): SINGLE AGENT ACTIVITY, DEVELOPMENT OF COMBINATION TREATMENT AND REDUCING SIDE EFFECTS

L.C. Pronk, G. Stoter and J. Verweij

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ABSTRACT

Docetaxel is a new semi-synthetic taxoid, which acts as an antimicrotubule agent and is now clinically available. Clinical studies of docetaxel as a single agent and in combination with other cytotoxic drugs reveals response rates in a number of solid tumor types. Docetaxel appears to have great potential in advanced breast cancer in first- or second-line chemotherapy.

The dose-limiting toxicity is an early and short-lasting neutropenia. Fluid retention is a cumbersome, sometimes disabling, side effect. Other side-effects are usually mild and include alopecia, myalgia, mucositis, neuropathy, hypersensitivity reaction, nail changes and cutaneous reactions.

INTRODUCTION

The taxanes are a new class of drugs that exert antitumor activity through a unique mechanism. In the late 1960s screening programs conducted by the National Cancer Institute revealed that an extract from the bark of the Pacific Yew, *Taxus Brevifolia*, exhibited antitumor activity against murine tumor models. That discovery led to the isolation and characterization of paclitaxel (Taxol), the active component of this extract (1,2). Because of the scarcity of the drug, the difficulties in its isolation, extraction and formulation, development of this antitumor agent has been relatively slow.

Several years ago, researchers from Rhône-Poulenc Rorer in conjunction with the French Centre National de la Recherche Scientifique developed docetaxel (Taxotere-RP 56976), a semisynthetic analog of paclitaxel using a precursor extracted from the needles of the European Yew, *Taxus Baccata* a renewable source (3). This review will focus on the development of docetaxel, summarizing preclinical and clinical data.

BIOCHEMISTRY AND MECHANISM OF ACTION

Docetaxel is prepared from 10-deacetyl baccatin III, a noncytotoxic precursor extracted from the needles of the European Yew, *Taxus baccata*. That precursor is then esterified with the synthetic side chain (3,4,5). Docetaxel has a chemical formula of $C_{43}H_{43}NO_{14}$ and a molecular weight of 807,9 (figure 1). It is insoluble in water, but soluble in 0.1 N hydrochloric acid, chloroform, dimethylformamide, 95%-96% v/v ethanol, 0.1 N sodium hydroxide and methanol. The formulation used in the most recent clinical studies consists of 100% polysorbate 80.

Microtubules are among the most strategic subcellular targets of anticancer agents. Like DNA, microtubules are ubiquitous to all eukaryotic cells. Microtubules are composed of tubulin dimers, consisting of an alpha and a beta subunit protein, that polymerize and, with numerous microtubule-associated proteins (MAPs), decorate the exterior wall of the hollow microtubule structure (6). There is continuous dynamic equilibrium between tubulin dimers and microtubules, i.e. a continuous balance between polymerization and depolymerization. Although their principal function is the formation of the mitotic spindle during cell division, microtubules are also involved in many vital interphase functions, including the maintenance of shape, motility, signal transmission and intracellular transport (7-10).

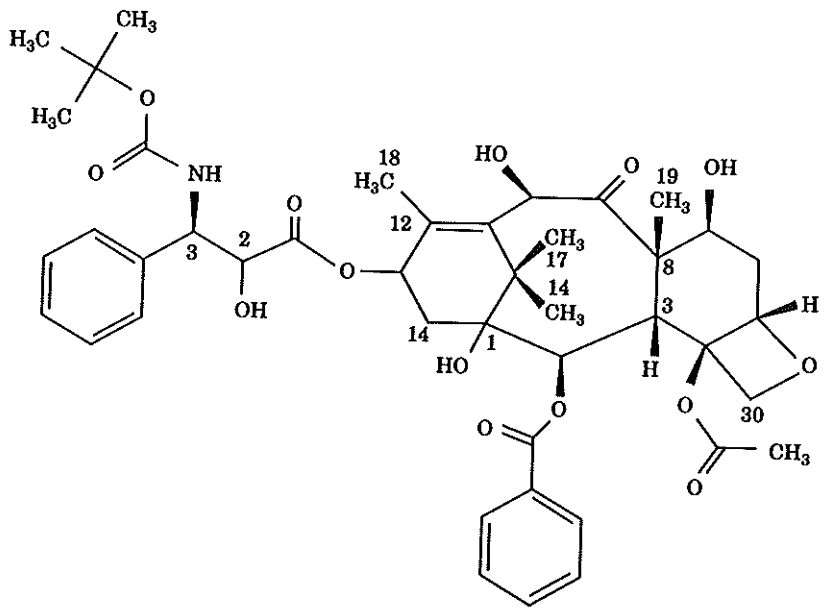
Many of the unique pharmacologic interactions of drugs with microtubules relate to the dynamic equilibrium (7,11). Any disruption of the equilibrium within the microtubule system would be expected to disrupt cell division and normal cellular activities in which microtubules are involved.

Taxanes bind preferentially and reversible to the N-terminal 31 amino acids of the beta-tubulin subunit in the microtubules rather than to tubulin dimers (12-16). Unlike other antimicrotubule drugs, such as vinca alkaloids that induce the disassembly of microtubules and inhibit polymerization, the taxanes promote the polymerization of tubulin into stable microtubules and

inhibit microtubule depolymerization, thereby inducing the formation of stable microtubule bundles (17-20). This disruption of the normal equilibrium ultimately leads to cell death.

Docetaxel generates tubulin polymers that differ structurally from those generated by paclitaxel (21). Unlike paclitaxel it does not alter the number of protofilaments in the microtubules (22).

FIGURE 1: CHEMICAL STRUCTURE OF DOCETAXEL



In vitro cytotoxicity

The antiproliferative action of docetaxel against a variety of freshly explanted tumor specimens using an *in vitro* soft agar cloning system was studied in final concentrations of 0.025-10 μg/ml in short term (1 hour) or continuous incubations (14 days) (23). Docetaxel had a significant concentration-dependent effect on the frequency of growth-inhibition in breast cancer, non-small cell lung cancer, melanoma, ovarian cancer, and

colorectal cancer. This was confirmed in a similar study using final concentrations of 0.04, 0.4 and 4.0 μmol/l (24). Again a concentration-dependent anti-tumor cell activity for both drugs was shown. All the types of tumor cells tested showed a response, even those resistant to conventional antineoplastic agents. Statistical analysis showed that docetaxel was significantly more active than cisplatin, doxorubicin, 5-fluorouracil and Interferon-α.

Riou *et al.* compared the cytotoxicity of docetaxel and paclitaxel in several murine (P388, SVras) and human cell lines (Calc 18, HCT 116, T24, N417, KB) (25). Docetaxel was found to be more potent than paclitaxel (1.3-12 fold), a result which could be explained by its higher affinity than paclitaxel for microtubules. Docetaxel is more cytotoxic on proliferating than on non-proliferating N417 cells and does not inhibit cellular DNA, RNA and protein synthesis. Docetaxel showed partial cross-resistance on the P-glycoprotein resistant P388/DOX cell line, but no evidence of cross-resistance was observed on either Calc 18/AM or P388/CPT5 cell lines, in which topoisomerase II and -I activities are modified.

Using the sulforhodamine B assay, Kelland and Abel studied the cytotoxic properties of docetaxel in nine ovarian carcinoma cell lines, three of which were rendered resistant to platinum derivates (26). The drug was much more cytotoxic than cisplatin, etoposide and doxorubicin in these cell lines. No cross-resistance with docetaxel was found in any of the cell lines with acquired resistance to platinum.

In vivo activity

Docetaxel has been studied in many murine tumor models and human tumor xenografts. In subcutaneous (s.c.) B16 melanoma docetaxel administered intravenously was found to be highly active (27). It was also active against MX-1 mammary cancer (28) and C38 colon carcinoma (29), while it induced a 100% cure rate for early-stage disease and complete regressions of advanced-stage tumors in CX-1 colon carcinoma and LX-1

lung carcinoma (29). In addition, docetaxel was active against s.c. early-stage pancreatic ductal adenocarcinoma (PO3) and s.c. colon adenocarcinoma 51 (C51), and in the xenografted KM 20L2 colon carcinoma, SK MEL-2 melanoma and OVCAR-3, HOC 8, HOC 10 and HOC 22 ovarian carcinomas (28,30). Other investigators found that docetaxel's activity in five human ovarian cancer lines appeared to be more effective than cisplatin, cyclophosphamide or doxorubicin (31). Docetaxel had a lesser degree of activity against Lewis lung carcinoma, Glasgow osteogenic sarcoma and the L1210 and P388 leukemias (27). It appears to be a schedule-independent drug in view of the fact that its administration schedule does not markedly influence the total dose that can be administered (27).

Preclinical toxicology

Preclinical toxicology studies of docetaxel were performed in mice and dogs for the single-dose schedule and the daily-times-five administration schedule. Docetaxel was formulated initially in a 50:50 polysorbate (PS) 80: ethanol solution at a maximum of 50 mg/ml. A solution of 10 mg/ml was used for the toxicology studies in dogs while a 15 mg/ml solution was used for the initial phase I studies in humans. A second formulation which is presently used consists of polysorbate 80 in a 40 mg/ml solution (32). Acute toxicity studies using a single intravenous dose schedule in mice showed that the LD10 was 345 mg/m^2 (303-390 mg/m^2) and the LD50 was 414 mg/m^2 (378-450 mg/m^2). In dogs the toxic dose low (TDL) was 15 mg/m^2 and the LD50 was 50 mg/m^2. Phase I trials of docetaxel in humans were started with a dose level based on one-third of the TDL in dogs: 5 mg/m^2. The main toxic effects of docetaxel were evident in tissues with high cell turnover, most of which were reversible. In mice cumulative and reversible neurotoxicity was seen. Dogs experienced hypotension which was thought to be related to PS80. Toxicity in mice and dogs was more pronounced in the daily-times-five administration schedule (33).

Preclinical pharmacology

A rapid, selective and reproducible high-performance liquid chromatographic (HPLC) assay to determine docetaxel levels in biological fluids was developed for preclinical pharmacokinetic evaluations in mice and dogs (33-35).

The drug distribution was biphasic, with α- and β-half lives of 7 minutes and 1.1 hour respectively. Maximum plasma concentrations in mice were proportional to dose. Pharmacokinetics appeared linear. Plasma clearance of drug from the body was 2.2 l/h/kg with a volume of distribution at a steady state of 2.2 l/kg. The AUC at doses of 13-62 mg/kg ranged from 4.5 to 29.6 μg/ml/h.

After the administration of radiolabelled docetaxel to mice, radioactivity diffused rapidly into all tissues except the central nervous system, with highest levels seen in liver, bile, intestines and gastric contents. Plasma protein binding in mice ranged from 76-89%. Elimination of docetaxel was virtually complete at 96 h after administration. The primary route of elimination of radiolabelled docetaxel in both the dog and mouse was by hepatic extraction and biliary excretion. Urinary excretion was $<10\%$ and pulmonary excretion was virtually absent (36).

PHASE I CLINICAL TRIALS ON SINGLE AGENT DOCETAXEL

Phase I studies on docetaxel were performed using different schedules of drug administration (37-42). The details of these studies are shown in Table 1. Throughout these trials the major dose limiting toxicity (DLT) was neutropenia that appeared to be short-lasting, dose-dependent, schedule-independent and non-cumulative. Another important side-effect was mucositis that was characterized by diffuse ulceration of the lips, tongue and oral cavity. The appearance of mucositis correlated with the granulocyte count nadir, and was seen more often with longer durations of infusion. In these studies higher rates of febrile neutropenia were observed than in the studies not associated with mucosal breakdown.

Other toxic reactions consisted of infrequent hypersensitivity reactions, mild paresthesias, general alopecia, nausea, vomiting, diarrhea, skin reactions (maculopapular eruptions with desquamation, erythema, nail changes) and fluid retention. Cardiac toxicity was not reported.

Responses were observed in different tumor types like breast cancer, ovarian cancer, adenocarcinoma of unknown primary, pancreatic carcinoma, small cell and non-small cell lung cancer (32). For phase II studies the recommended dose and schedule was 100 mg/m^2 given as a 1-hour infusion every 3 weeks. Because of the infrequency of serious hypersensitivity reactions phase II studies were initially performed without routine premedication. Prophylactic antiemetics are not indicated as docetaxel is not highly emetogenic.

TABLE 1: PHASE I STUDIES ON SINGLE AGENT DOCETAXEL

Schedule	MTD (mg/m^2)	DLT	Ref.
1-2h every 3 wks	115	neutropenia, skin	37
6h every 3 wks	100	febrile neutropenia, skin, oral mucositis	39
24h every 3 wks	90	febrile neutropenia, skin, oral mucositis	40
1h, days 1 and 8, every 3 wks	55x2	neutropenia, asthenia	38
1h, days 1-5, every 3 wks	16x5	febrile neutropenia, mucositis	41

MTD = Maximum Tolerated Dose; DLT = Dose Limiting Toxicity

PHASE I CLINICAL TRIALS ON COMBINATIONS OF DOCETAXEL WITH OTHER DRUGS

Phase I studies combining docetaxel with other cytotoxic drugs are either only recently completed or still ongoing (Table 2). The feasibility of combining high doses of docetaxel and cisplatin has recently been reported (43-45). Verweij *et al.* (43) performed a phase I study with docetaxel and cisplatin using two different treatment schedules, one consisting of docetaxel given as a 1-hour infusion followed by cisplatin as a 3-hour infusion (schedule A), and the second cisplatin followed by docetaxel (schedule B). Cycles were repeated every 3 weeks. Cisplatin doses ranged from 50-100 mg/m^2 while docetaxel doses ranged from 55-100 mg/m^2.

TABLE 2: PHASE I STUDIES ON COMBINATION OF DOCETAXEL WITH OTHER DRUGS

Schedule		Recommended dose (mg/m^2)	DLT	Ref
docetaxel→ cisplatin→	cisplatin (A) docetaxel (B) q 3 wks.	docetaxel 85-100 cisplatin 75	neutropenia	43
docetaxel→	cisplatin q 3 wks.	docetaxel 75 cisplatin 75	neutropenic fever	44
docetaxel→	cisplatin q 3 wks.	docetaxel 75 cisplatin 75-100	neutropenia	45
adriamycin→ docetaxel→	docetaxel adriamycin q 3 wks.	not reached	neutropenia	47

Fifty-two patients were entered of whom twenty-one patients had had prior chemotherapy, seven prior radiotherapy and eight both. Leuko- and granulocytopenia were common (92%, grade 3-4 68%), short-lasting and docetaxel dose-dependent; related infections occurred in 7%. Other toxicities included alopecia, nausea and vomiting, diarrhea and mucositis, most of them being mild. Granulocytopenia and mucositis were significantly more pronounced during schedule B. Responses were observed in both treatment schedules. Docetaxel did not change the pharmacokinetics of cisplatin (46). A dose of 85-100 mg/m^2 of docetaxel combined with 75 mg/m^2 of cisplatin appeared manageable with docetaxel being administered before cisplatin. Zalcberg *et al.* (44) treated sixteen patients with non-small cell lung cancer who had had no prior chemotherapy. Docetaxel was administered as a 1-hour infusion immediately followed by cisplatin as a 1-hour infusion in a 3-weeks cycle. Docetaxel and cisplatin doses ranged from 50-100 mg/m^2 and 75-100 mg/m^2 respectively. The dose limiting toxicity was neutropenic fever. The recommended dose was 75 mg/m^2 of both docetaxel and cisplatin. Another phase I-II study combining cisplatin and docetaxel in twenty-five patients with non-small cell lung cancer previously untreated with chemotherapy, was performed by Cole *et al.* (45). Docetaxel was administered as a 1-hour infusion followed by cisplatin as a 30 minutes infusion every 3 weeks. Docetaxel and cisplatin doses ranged from 75-85 mg/m^2 respectively. Granulocytopenia was the only dose-limiting toxicity. Dose levels of 75 mg/m^2 of docetaxel combined with 75-100 mg/m^2 of cisplatin are recommended for further studies.

The combination of docetaxel with adriamycin has been studied as first-line chemotherapy in patients with metastatic breast cancer (47). In this study adjuvant therapy is allowed if there was a treatment-free interval of at least 12 months. Adriamycin is given as an i.v. bolus followed by docetaxel as a 1-hour infusion every 3 weeks. Dose levels for adriamycin and docetaxel ranged from 40-60 mg/m^2 and 40-50 mg/m^2 respectively. At these dose levels the main toxicity was grade 4

neutropenia in fourteen out of sixteen cycles. No other toxicities more severe than grade 2 were observed except alopecia. The study will be continued at a dose level of 50 mg/m^2 of adriamycin followed by 60 mg/m^2 of docetaxel. In breast cancer more studies are ongoing combining docetaxel with 5-fluorouracil, cyclophosphamide and the combination of these two agents. For all tumor types phase I studies are being performed combining docetaxel with either cisplatin, 5-fluorouracil, cyclophosphamide or ifosfamide (Table 3).

TABLE 3: ONGOING PHASE I COMBINATION STUDIES

PHASE I ALL TUMOR TYPES
Combination:
docetaxel/cisplatin
docetaxel/5FU
docetaxel/cyclophosphamide
docetaxel/ifosfamide
PHASE I BREAST CANCER
Combination:
docetaxel/doxorubicin
docetaxel/5FU
docetaxel/cyclophosphamide
docetaxel/cyclophosphamide/5FU

PHASE II CLINICAL TRIALS

Phase II studies on docetaxel have been performed or are still ongoing in many tumor types. In most of these studies the same dose-schedule of 100 mg/m^2 as a 1-hour infusion every 3 weeks was used. Many of the data are derived from abstracts and should therefore be considered as preliminary.

Breast cancer

In first-line chemotherapy for metastatic or locally advanced breast cancer, response rates in four independent studies varied from 57 to 87% with a docetaxel dose of 100 mg/m^2 every 3 weeks (48-51), which is even more interesting if one takes into account the total number of patients and the fact that three of the studies were multicenter studies that usually tend to have lower response rates than single center studies. The EORTC Clinical Screening Group performed two consecutive phase II studies with two dose levels of docetaxel: 100 mg/m^2 as a 1-hour infusion and 75 mg/m^2 respectively. The response rate at a docetaxel dose of 100 mg/m^2 was 69% and decreased to a response rate of 52% at a dose of 75 mg/m^2. There was no difference between the side-effects except for grade 4 neutropenia (Table 4).

The response rate of docetaxel in second-line chemotherapy, being 55% is only slightly lower than in first-line chemotherapy (52,53). Furthermore docetaxel frequently induces responses in liver metastases (53, 54). Preliminary results indicate clinical activity in paclitaxel resistant metastatic breast cancer (53). In a phase II study of the EORTC Breast Cancer Study Group docetaxel was administered at a dose of 50 mg/m^2 on day 1 and 8 every 3 weeks. Patients were randomized between prophylactic oral antihistamine with or without methylprednisolone. Preliminary response evaluation in 52 patients yielded a response rate of 34% (55). Regarding the response rate and safety profiles of the different dose-schedules one might conclude that docetaxel at a dose of 100 mg/m^2 as a 1-hour infusion every 3 weeks is the most appropriate schedule.

Ovarian cancer

Docetaxel at the dose of 100 mg/m^2 showed substantial activity in patients with advanced ovarian cancer refractory to cisplatin or carboplatin therapy in four different studies (56-59). In 195 patients an overall response rate of 28.7% was reported. Piccart *et al.* conducted a

phase II study in patients with advanced epithelial ovarian cancer who had disease relapse or disease progression within 12 months of the last administration of a first-line or second-line platinum-based regimen (57).

TABLE 4: EVALUATION OF 2 DOSES OF DOCETAXEL AS FIRST-LINE IN BREAST CANCER

	docetaxel dose mg/m^2	
	75	100
Number of patients	31	32
Efficacy results:		
Response rate (%)	52	68
CR (%)	13	16
Median duration of response (wks)	34	44
Safety results:		
Neutropenia gr 4 (%)	53	69
Infection gr 3 (% cycles)	0	0
Hypersensitivity gr 3 (% cycles)	3	3
Skin gr 3 (%)	3	12
Neurosensory gr 3 (%)	2.6	-
Severe fluid retention (%)	13	17

Of the 90 eligible patients 42 patients started docetaxel within 4 months of their last platinum course, and 48 patients within 4-12 months of completing platinum treatment. The most important toxicity was grade 3 or 4 neutropenia (90%), however the percentage of patients with neutropenic fever requiring hospitalization for the administration of parenteral antibiotics was only 8%. Alopecia and fatigue were also frequent side-effects (83 and 82% respectively). Seventy-six patients were assessable for tumor response. The overall response rate was 23.6% with a median progression-free survival of 3.9 months and a median overall survival of 8.4 months.

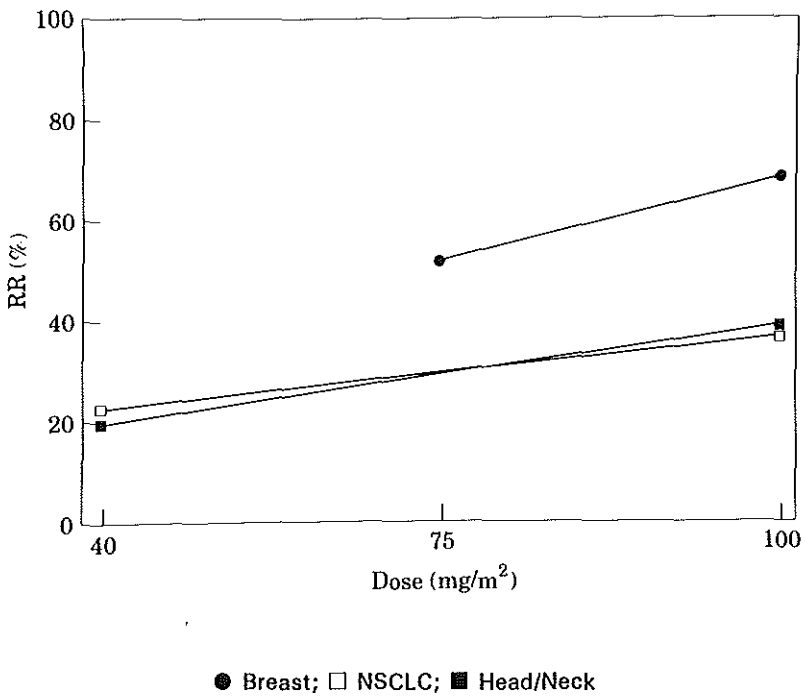
Francis reported a median response duration of 5 months (range 3 to 9 months). The time to major response varied from 3 weeks to 3 months. The median survival duration for all patients from study entry was 8 months (59). Recently a phase II study in patients with advanced ovarian carcinoma with platinum-free interval of more than 12 months was completed. In 40 evaluable patients three complete responses (CRs) and 10 partial responses (PRs) were recorded (objective response rate 32.5%) (60).

Other tumors

Docetaxel as a single agent at a dose of 100 mg/m^2 every 3 weeks showed activity in phase II studies in non-small cell lung cancer, yielding a response rate of 36% (61-63). Cerny *et al.* reported a median response duration of 36 weeks (range 15-48 weeks) and a median survival of 11 months. Fossella reported a response duration that varied from 19 to 34 weeks. Kawahara *et al.* performed phase II studies of docetaxel at a dose of 60 mg/m^2 every 3 weeks yielding response rates ranging from 20 to 25% and a median survival of 41-43 weeks (64). Interestingly, in second-line chemotherapy in non-small cell lung cancer, docetaxel retains its activity. A response rate of 26% was reported by Fossella (65) in cisplatin-refractory patients, which is an important observation in this group of patients with an extremely poor prognosis. Phase II studies in non-small cell lung cancer combining docetaxel with cisplatin are ongoing (66,67). Le Chevalier *et al.* used a treatment schedule of docetaxel 75 mg/m^2 and cisplatin 100 mg/m^2 on days 1,21,42 and then every 6 weeks in previously untreated patients. In 24 evaluable patients six partial responses (PRs) were observed. The main toxicities were febrile neutropenia, documented sepsis and a hypersensitivity reaction (66). Zalcberg *et al.* administered docetaxel and cisplatin both at a dose of 75 mg/m^2 every 3 weeks to patients untreated with chemotherapy. In 17 evaluable patients nine PRs were observed (53%) (67). Grade 4 toxicities included febrile neutropenia and diarrhea.

In head and neck cancer, docetaxel at a dose of 100 mg/m^2 every 3 weeks is very active in first-line chemotherapy. Response rates as high as 32 and 48% were reported by Catimel and Dreyfuss, respectively (68,69). Fujii *et al.* performed a phase II study of docetaxel at a dose of 60 mg/m^2 every 3 to 4 weeks in patients with squamous- and non-squamous cell carcinoma of the head and neck (70).

FIGURE 2: DOSE-RESPONSE CURVE OF DOCETAXEL IN THREE TUMOR TYPES



A response rate of 20% was seen in previously untreated patients while 15,8% of the previously treated patients responded. These data suggest a dose-response relationship for docetaxel (Figure 2). In addition,

docetaxel appears to be an active drug for melanoma, gastric cancer, pancreatic cancer, small cell lung cancer and cisplatin-refractory transitional cell cancer (Table 5).

TABLE 5: PHASE II STUDIES IN VARIOUS TUMOR TYPES

Tumor type	docetaxel dose (mg/m^2)	N	RR%	Ref.
First-line				
Head/neck	60	ND	20	70
	100	60	38	68,69
NSCLC	60	143	22	64
	100	173	36	61-63
Gastric cancer	100	33	24	71
Upper gastrointestinal tract	100	22	14	72
Pancreatic cancer	100	28	25	73,74
Colorectal cancer	100	68	0	75-77
Melanoma	100	56	16	78,79
Renal cancer	100	43	5	80,81
Second-line				
Head/Neck	60		16	70
NSCLC	100	69	26	65
SCLC	100	28	25	82
Soft Tissue Sarcoma	100	29	17	83
Transitional cell carcinoma	100	20	20	84

ND: not done

SIDE EFFECTS

Many phase II studies have been performed now with docetaxel, most of them using a dosage schedule of 100 mg/m^2 given as a 1-hour infusion every 3 weeks. The most important side-effect is an early and short-lasting neutropenia which in 20% of the patients was complicated by infection (85). Alopecia is a common side-effect and usually universal. Fatigue is a frequent complaint starting a few days after docetaxel administration and ending around day 7. Nausea and/or vomiting are

relatively infrequent and are easily treated with conventional anti-emetics if necessary. Diarrhea and mucositis are usually mild in severity, the latter being treated and prevented adequately with frequent mouth-washes. Many patients complain of a change of taste sometimes leading to anorexia. Arthralgia and myalgia are infrequent but if they occur this is usually after a few days, lasting around 4 days. They may cause a lot of discomfort that in subsequent courses can be prevented or reduced in severity by the use of prophylactic analgesics such as paracetamol. Skin toxicities that have been described in phase II trials consist of changes in finger- and toenails and include thinning and ridging of the nail plates, onycholysis, subungual erythema and subungual haemorrhage. Specific mucocutaneous reactions include erythema, radiation recall, erythematous maculas, papules and plaques. Studies are ongoing addressing the question whether corticosteroid premedication reduces the incidence of this side-effect. The majority of hypersensitivity reactions to docetaxel occur during the first 2 cycles and almost always within minutes after the start of infusion (86). The overall incidence in treatments without premedication is approximately 25% (86-88). One of the most troublesome side-effects of docetaxel is the occurrence of fluid retention, which includes peripheral oedema, ascites or pleural fluid, or a combination of these. Fluid retention is sometimes associated with a significant weight gain. For docetaxel the fluid retention appears to be related to the cumulative dose, increasing in incidence at cumulative doses of $\geq$ 400 mg/m^2 (86-88).

A mild, dose-dependent, predominantly sensory neuropathy has frequently been reported. At cumulative dose levels about 600 mg/m^2 a patient may develop a severe and disabling neuropathy (89). Finally, cardiotoxicity was never documented in docetaxel treatment.

MEASURES TO PREVENT/REDUCE SIDE EFFECTS

The most important side-effect of docetaxel is an early and short-

lasting neutropenia (85). Until now growth factors have not been used as a standard prophylactic measure. In view of the relatively low incidence of febrile neutropenia, this approach still appears justifiable. However, specific instructions to patients and treating physicians will be required.

Fluid retention is a cumbersome and sometimes disabling side-effect. The EORTC Clinical Screening Group investigated whether prophylactic premedication consisting of dexchlorphreniramine 5 mg i.v. and ranitidine 50 mg i.v. 30 minutes before docetaxel administration plus prednisolone 130 mg orally 12 and 6 h before chemotherapy could reduce the incidence and severity of fluid retention (90). In 37 evaluable patients fluid retention occurred in 89.2% of the patients 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 to onset of fluid retention was 301 mg/m^2 and to treatment discontinuation due to fluid retention 698 mg/m^2. The investigators concluded that the above mentioned premedication failed to reduce and/or delay the incidence of fluid retention.

In phase II study of the EORTC Breast Cancer Study Group docetaxel was administered at a dose of 50 mg/m^2 on day 1 and 8 every 3 weeks, and patients were randomized between prophylactic oral antihistamine with or without methylprednisolone (55). Of the patients who received steroids 32% developed oedema, 32% developed new pleural effusion and 21% weight gain. In the patients who were not treated with steroids oedema occurred in 48%, pleural effusion in 44%, new pericardial effusion in 16% and weight gain in 32%. Steroids appeared to decrease the severity of the fluid retention phenomenon, although it remained a frequent reason for treatment discontinuation.

American data that have not been published yet indicate that with corticosteroid premedication fluid retention occurs after a median dose of 600 mg/m^2. The addition of $5HT_2$ blockers to the premedication schedule does not influence the occurrence in severity or frequency. A remarkable observation from the data base available at Rhône-Poulenc Rorer was that

patients who received a so-called venotonic drug were able to tolerate more courses of docetaxel. At this moment the value of a venotonic drug (hydroxy-ethylrutosiden) is tested in the prevention of docetaxel related fluid retention.

The application of premedication including corticosteroids has markedly reduced the incidence of hypersensitivity reactions (88) which can no longer be considered to be a major clinical problem. Reducing the infusion rate in the first minutes of docetaxel administration appeared to prevent hypersensitivity reactions even without corticosteroid premedication (unpublished data).

CLINICAL PHARMACOLOGY

Docetaxel disposition does not appear to be schedule-dependent. The area under the curve (AUC) increases in proportion to the administered dose of docetaxel, consistent with linear pharmacokinetics. At dose levels between 20 and 70 mg/m^2 plasma disappearance is biphasic, while at the highest clinical dose levels docetaxel disposition is triphasic (37). Phase I studies showed that both the end of infusion plasma drug concentration and the AUC showed large intersubject variations, although for individuals these two parameters correlated well (40,41). More than 90% of docetaxel is protein bound during the first 8 h post-infusion. A study with radiolabelled ^{14}C docetaxel demonstrated that 80% of the radioactive substance was excreted in faeces by day 7 while 5% was detected in urine during the first 6 h of collection (91).

Pharmacokinetic and pharmacodynamic studies on docetaxel were performed in four phase II studies (92). Patients were divided in three groups: patients with liver metastases and elevated alkaline phosphatase and/or elevated SGOT (group I), patients with liver metastases and normal liver enzymes (group II) and patients without liver metastases (group III). Of group I 73% had to be admitted for neutropenic fever. There was an

increased risk for leukopenia grade 4, mucositis and skin toxicity compared to the other two groups. Furthermore, the docetaxel clearance appeared to be reduced in patients with liver metastases and abnormal liver function.

Another pharmacokinetic analysis in 547 patients in 22 phase II studies demonstrated that interpatient variability of docetaxel clearance correlates with body surface area (BSA), α1-acid glycoprotein (AAG) plasma level and hepatic enzyme plasma levels (93). Pharmacokinetic/ pharmacodynamic analysis demonstrated that clearance variability is a strong predictor of the odds of grade 4 neutropenia and is weakly related to the risk of fluid retention. Clearance variability related to BSA is adequately accounted for by dosing docetaxel in mg/m^2. It was not possible to assess whether AAG influences pharmacodynamics through its effect on pharmacokinetics. No evidence was found of an increased odds of neutropenia grade 4 in the subpopulation of patients with elevated hepatic enzymes despite a 30% reduction in clearance. Nor do the data support a relationship between clearance and response rate in breast cancer and non-small cell lung cancer.

FUTURE PERSPECTIVES

Docetaxel is an important addition to the presently available classes of drugs. It has great potential in the treatment of breast cancer in first- and second-line chemotherapy. The preliminary evidence of antitumor activity in non-small cell lung cancer, head and neck cancer and soft tissue sarcoma in first- and second-line chemotherapy is extremely interesting, particularly in view of the generally disappointing results of chemotherapy for advanced disease in these tumor types. Several new studies are underway to investigate the value of docetaxel both as a single agent and in combination with other cytotoxic drugs for patients with these diseases.

More studies are needed to reduce the toxic effects of docetaxel. The

possible role of growth factors still has to be established. Fluid retention is a troublesome and sometimes disabling side-effect, that may be a reason for treatment discontinuation. The role of a venotonic drug (hydroxy-ethylrutosiden) in the prevention of fluid retention is under investigation.

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PHASE I AND PHARMACOLOGIC STUDY OF DOCETAXEL AND CISPLATIN IN PATIENTS WITH ADVANCED SOLID TUMORS

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ABSTRACT

Background and purpose

Docetaxel and cisplatin have shown significant activity against a variety of solid tumors, while their toxicity profiles are only partially overlapping. Therefore, it was considered worthwhile to pursue a combination regimen with these drugs. This phase I study was performed to assess the feasibility of the combination and to determine the maximum-tolerated-dose (MTD) and the side effects with an emphasis on sequence-dependent side effects.

Patients and methods

Patients who were not pretreated with taxanes or cisplatin derivatives and who had received no more than one prior combination chemotherapy regimen or two single-agent regimens were entered. Treatment consisted of docetaxel given as a 1-hour infusion followed by cisplatin as a 3 hours infusion (schedule A), or cisplatin followed by docetaxel (schedule B). Docetaxel doses ranged from 55-100 mg/m^2 and cisplatin doses from 50-100 mg/m^2.

Results

Leukocytopenia and granulocytopenia were common (overall, 90%; grade 3 or 4, 87%), short-lasting and docetaxel dose-dependent. Infections and neutropenic fever occurred in 10% and 4,5% of courses, respectively. Non-hematologic toxicities were mild to moderate and included alopecia, nausea, vomiting, diarrhea, mucositis, neurotoxicity, fluid retention and skin- and nail toxicity. There were no significant differences in pharmacokinetic parameters between schedule A and B. Tumor responses included one complete response (CR) and nine partial responses (PRs)

Conclusions

The dose levels docetaxel 100 mg/m^2 plus cisplatin 75 mg/m^2 and docetaxel 85 mg/m^2 plus cisplatin 100 mg/m^2 appeared to be manageable. At these dose levels the median relative dose-intensity was high and 81% and 88% of all cycles, respectively, could be given at full dose. Schedule A is advocated for further treatment.

INTRODUCTION

Docetaxel (Taxotere) (Rhône-Poulenc Rorer, Antony, France) is a new antimicrotubule agent that enhances polymerization of the tubulin into stable microtubules and inhibits microtubule depolymerization. This leads to a disruption of the equilibrium within the microtubule system and ultimately to cell death (1-3). The activity of docetaxel was studied in many murine tumor models, which showed that docetaxel was active against subcutaneous B16 melanoma (4), MX-1 mammary cancer (5), C38 coloncarcinoma, CX-1 colon carcinoma, LX-1 lung carcinoma (5,6), PO3 pancreatic carcinoma, and OVCAR-3, HOC 8, HOC 18, and HOC 22 ovarian carcinomas (5,7). In the phase I studies on single-agent docetaxel, responses were reported in various tumor types such as ovarian cancer, breast cancer, and non-small cell lung cancer (8-13). The main dose-limiting toxic effect was an early-onset, short-lasting, dose-dependent, schedule-independent and non-cumulative neutropenia. Other side effects were mild and included paresthesias, infrequent hypersensitivity reactions, general alopecia, nausea, vomiting, diarrhea, fluid retention and skin reactions. Based on these studies, the recommended dose and schedule for phase II studies on docetaxel was 100 mg/m^2 given as a 1-hour infusion every 3 weeks. Phase II studies on docetaxel showed activity in breast cancer (14-18), non-small cell lung cancer (19-21), head and neck cancer (22), gastric cancer (23), melanoma (24), soft tissue sarcoma (25) and pancreatic cancer (26).

Cisplatin is a highly effective drug for the treatment of, among others,

testicular tumors and ovarian-, bladder- and head and neck cancers. The combination of docetaxel and cisplatin could be of major relevance, since both drugs are effective in a multitude of solid tumors and their toxicity profiles only marginally overlap.

We performed a phase I study of the combination of docetaxel and cisplatin with the following objectives: 1) to determine the maximum-tolerated dose (MTD), 2) to characterize the toxic effects, 3) to determine if the drug administration sequence can influence the tolerance of the combination, 4) to propose a safe schedule: dose, sequence of drug administration, and time interval for further phase II evaluation in solid tumor patients, 5) to determine the pharmacokinetic profile and protein-binding of docetaxel and cisplatin when administered in combination, and 6) to report any observed antitumor effect of the docetaxel-cisplatin regimen in this group of patients.

MATERIALS AND METHODS

Eligibility

Only patients with histologically documented solid tumors for which no therapies with greater potential benefit than docetaxel and cisplatin existed were candidates for this study.

Eligibility criteria further included the following: 1) age $\geq$ 18 years and $\leq$ 75 years; 2) World Health Organization (WHO) performance status 0-2; 3) life expectancy of at least 12 weeks; 4) no more than one prior combination regimen or more than two single-agent regimens; 5) off previous anticancer therapy for at least 4 weeks (6 weeks in case of Mitomycin, nitrosoureas, or extensive radiotherapy); 6) no prior treatment with cisplatin derivatives or taxoid drugs; 8) adequate bone marrow- (neutrophil count $\geq 2 \times 10^9$/L, and platelet count $\geq 100 \times 10^9$/L), hepatic (total bilirubin $\leq$ 1.25 times and ASAT $\leq$ two times the upper normal limits), and renal (creatinine concentration $\leq$ 120 μmol/L or creatinine clearance $\geq$ 60 mL/min) functions; 9) absence of symptomatic peripheral

neuropathy greater than grade 0 according to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) (27). All patients had to give written informed consent.

Drug administration

Docetaxel was supplied by Rhône-Poulenc Rorer (Antony, France) as a concentrated sterile solution that contained 40 mg/mL in a 2-mL vial in polysorbate 80 (Tween 80). The appropriate amount of the drug to be administered to the patient was diluted in 5% dextrose solution (or 0,9% saline serum) so that the maximum docetaxel concentration was 1 mg/mL. The drug was administered to the patients as a 1-hour infusion.

Cisplatin was administered as a 3-hour infusion diluted in 1 L of 0.9% saline. Before cisplatin administration, patients were hydrated with 1 L of 0.9% saline infused over 3 hours and subsequent to cisplatin with 3 L of 0.9% saline infused over 18 hours. Antiemetics included 8 mg intravenous (IV) Ondansetron or 5 mg i.v. Tropisetron and 10 mg i.v. bolus Dexamethasone just before the cisplatin infusion. Initially, no premedication for hypersensitivity reactions was given. However, during the study, data from extensive phase II studies on single-agent docetaxel became available that suggested beneficial effects of additional medication to prevent side effects. The final combination of prophylactic drugs included Dexamethasone 10 mg given as i.v. bolus 24 and 6 hours before and 24 hours after docetaxel administration, while the antihistamine clemastine fumarate was given orally at a dose of 2 mg 30 minutes before docetaxel administration.

Dosage

The docetaxel and cisplatin doses were escalated according to a preestablished schedule and according to the toxicities observed at the previous dose level after a minimum of three patients had tolerated the previous dose. Once side effects of CTC grade $\geq$ 3 other than myelosuppression had been reported, at least an additional three patients

were entered at that dose level. Dose-limiting toxicity was defined as CTC greater than grade 2 toxicity (excluding myelotoxicity) noted in three or more patients at a given dose level. For myelosuppression, dose-limiting toxicities were defined as follows: 1) granulocyte count less than 0.5 x 10^9/L for more than 7 days or less than 0.5 x 10^9/L with fever $\geq$ 38.5°C requiring i.v. antibiotics; and no recovery to $\geq$ 1.5 x 10^9/l on day 21 of treatment; 2) platelet count less than 25 x 10^9/L without recovery to $\geq$ 50 x 10^9/L on day 21 of treatment occurring in more than 25% of courses at a given dose level.

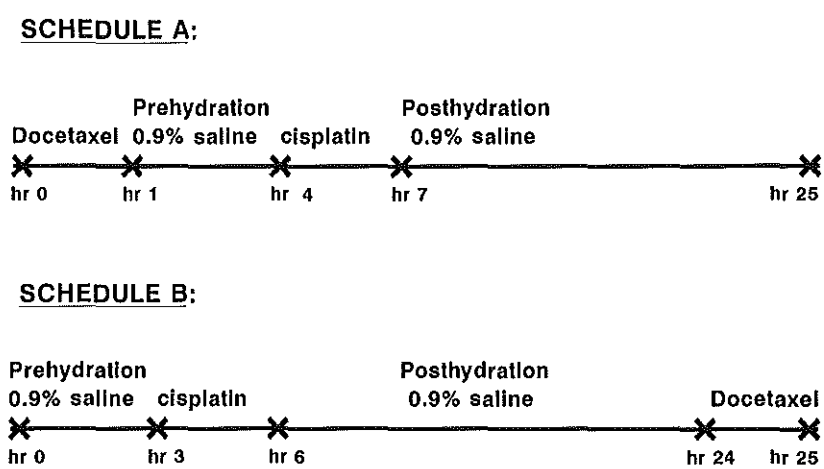
The MTD was defined as the dose to be used for further phase II evaluation in solid tumor patients, which could be safely administered to a patient while producing tolerable, manageable, and reversible toxicity. At least six patients were to be studied at the MTD. The starting doses of docetaxel and cisplatin were 55 mg/m^2 and 50 mg/m^2 respectively. At first, dose escalation of docetaxel was performed with the dose of cisplatin being fixed. Two doses of cisplatin were assessed in parallel, but priority for patient inclusion was always given to the dose level with the highest docetaxel dose. Dose levels of docetaxel/cisplatin studied were 70/50, 85/50, 100/50, 55/75, 70/75, 85/75, 100/75, 75/100 and 85/100 mg/m^2. Two MTDs could be determined, one with the highest docetaxel dose with cisplatin 75 mg/m^2, the other with the highest docetaxel dose with cisplatin 100 mg/m^2.

Drug sequence

Dose escalation was initially performed with docetaxel preceding cisplatin (schedule A) with a 1-hour interval between the end of the docetaxel infusion and the start of the cisplatin infusion (Figure 1). When the MTDs and doses to be used for further phase II evaluation were defined with schedule A, the dose level just below the MTD was reassessed with cisplatin preceding docetaxel (schedule B). On this schedule, the interval between the end of the cisplatin infusion and the start of the docetaxel infusion was 18 hours. The given intervals were

derived from the optimal intervals in preclinical studies (M. Bissery, personal communication). When acceptable toxicities were observed, further dose-escalation was pursued with schedule B.

FIGURE 1: DRUG ADMINISTRATION SEQUENCE



Pretreatment and follow-up studies

Before the start of treatment, a history was taken and physical examination, neurologic examination, laboratory studies, ECG, chest x-ray, and an audiogram were performed. If appropriate, computed-tomographic scans were performed for tumor measurements. Laboratory studies included a complete blood count, differential WBC count, electrolytes (sodium, potassium, chlorine, biocarbonate, magnesium, and calcium), creatinine, urea, alkaline phosphatase, lactate dehydrogenase, AST, ALT, bilirubin, protein, albumin, glucose, uric acid, urinalysis, and creatinine

clearance. History, physical examination, screening neurologic examination, toxicity scoring (according to NCI CTC), and laboratory studies were repeated weekly. Complete blood counts were obtained twice a week and every 2 days in case of febrile neutropenia. Every 3 weeks, chest x-ray and ECG were repeated. Formal tumor measurements and detailed neurologic examinations, including Vibration Perception Threshold (VPT) and, if necessary, electromyography, were performed after every two courses of chemotherapy. Standard WHO response criteria (28) were used.

Pharmacologic studies

For docetaxel and cisplatin, pharmacokinetics and protein-binding studies were performed. For the analysis of docetaxel, 3 mL blood samples were taken from the arm opposite to the infusion site immediately before the start of the infusion, 30 minutes after start of the infusion, at the end of the infusion, and then at 5,10,20,30,60, and 90 minutes and at 2, 4, 6, 8, 12, and 24 and, whenever possible, 36- and 48-hour post-infusion.

For the protein-binding studies of docetaxel, 3-mL blood samples were collected immediately before infusion, at the end of the infusion, and 20 minutes, 1, 2, and 6-hour post-infusion. For pharmacokinetics and protein-binding studies of cisplatin, blood samples were collected immediately before infusion (8 mL) and 1, 2, 3, 4, 5, 6, 8, 10 and 21 hours after the start of infusion (4 mL). For cisplatin, both total and non-protein- bound plasma concentrations were determined.

Assays for pharmacokinetics were reported elsewhere (29, 30). Pharmacokinetic parameters were calculated using the least-squares regression method (31). The Siphar software package was used (release 4.0, Simed, Créteil, France).

Statistical analysis

To evaluate the neurological toxicity, the incidence of neurologic

signs and symptoms at the first evaluation after the last cycle was determined. Patients with preexisting signs or symptoms were not included in these analyses. The change in sensory sum-score and the VPT post-pre ratio were calculated for each patient. Spearman rank correlations were calculated to describe the strength of the association between cumulative doses of cisplatin and docetaxel and the increase in sensory sum-score and the VPT post-pre ratio. Because of the skewed distribution of the VPT, the geometric mean was used to determine the mean of the VPT post-pre ratio. For the sensory sum-score, the arithmetic mean was calculated. For differences in side effects between schedule A and B, the Mann-Whitney test was used.

RESULTS

Sixty-six patients were entered onto this study. Two patients were never treated, as they appeared to have an infection at baseline. Patients characteristics (64 patients treated) are listed in Table 1. The large number of patients with colorectal carcinoma (23 patients) and cancer of unknown primary site (13 patients) reflected the lack of available second- (and even first-) line chemotherapy treatment for these patients and the use of non-cisplatin-containing regimens in first line for these cancer types.

Table 2 lists the doses studied, number of patients entered at each dose level, number of courses at each dose level, and range of courses per individual patient. Fourteen patients were treated at two dose levels because of dose reduction due to various toxicities. The numbers in parentheses represent the number of patients who were initially treated at a higher dose level and underwent dose reduction.

TABLE I: PATIENT CHARACTERISTICS

Characteristic	No. of Patients
Patients treated	64
Age, years	
Median	53
Range	(21-74)
Sex	
Male	33
Female	31
WHO performance status	
0	20
1	42
2	2
Prior treatment	
No prior treatment	15
chemotherapy: none	33
One regimen	26
Two regimens	5
Exclusive radiotherapy	2
Exclusive surgery	9
Histologic diagnosis	
Colon or rectal cancer	23
Unknown primary cancer	13
Breast cancer	5
Head and neck cancer	5
Soft Tissue Sarcoma	2
Ewing Sarcoma	2
Stomach cancer	5
Lung (non-small-cell) cancer	3
Melanoma	2
Pancreatic cancer	1
Peritoneal cancer	1
Urothelial cell cancer	1
Renal	1

These patients were evaluated for toxicity at the higher dose level; once dose reduction had taken place, patients were evaluated for toxicity at the lower dose level. The two patients who never received treatment were respectively planned at dose levels 10A (docetaxel 85 mg/m^2 and cisplatin 100 mg/m^2) and 11 (docetaxel 100 mg/m^2 and cisplatin 100 mg/m^2). A total of 244 courses of docetaxel in combination with cisplatin were given. One course was not fully assessable at dose level 11 (docetaxel 100 mg/m^2 and cisplatin 100 mg/m^2), because the patient died of sepsis on day 3. A total of 243 courses were assessable for toxicity. Of 201 courses, the duration of the granulocyte nadir could be determined in close detail.

TABLE II: PATIENT ACCRUAL

Dose level	Total dose (mg/m^2)				No. of patients treated (*)	Total Cycles No./Range
	Schedule A		Schedule B			
	TXT	CDDP	CDDP	TXT		
1A	55	50			3	14 (4-6)
2A	70	50			3	18 (6-6)
3A	85	50			3	12 (1-6)
4A	100	50			4	10 (2-4)
5A	55	75			3(+3)	26 (4-8)
6A	70	75			4(+2)	15 (1-6)
6B			75	70	4(+2)	14 (1-6)
7A	85	75			4(+5)	24 (2-6)
7B			75	85	4(+1)	20 (2-6)
8A	100	75			9	31 (2-6)
8B			75	100	7	17 (1-6)
9A	75	100			8(+1)	21 (1-6)
10A	85	100			7	22 (1-6)
11A	100	100			1	1
Total					64	244 (1-8)

* number of patients initially treated at a higher dose level.

No dose-limiting toxicities (as described earlier) were observed for cycle 1 at the dose levels 1A to 7A and 7B, which allowed a quick dose escalation. Dose-limiting toxicities were reported for cycle 1 at the following dose levels: infection grade 4 with sepsis (one patient) at dose level 8A; infection grade 4 with sepsis (one patient), and nephrotoxicity (creatinine grade 2, one patient) at dose level 10A; grade 4 neutropenia lasting 11 days (one patient), diarrhea grade 3 (one patient) and *Escherichia coli* sepsis with hepatotoxicity (AST/ALT) grade 3 (one patient) at dose level 8B. A septic death was reported at dose level 11 (docetaxel and cisplatin 100 mg/m^2). No other septic death was reported during this study.

Hematologic toxicities

Leukocytopenia and granulocytopenia were common, occurring in 90% of the courses. Tables 3 and 4 list the relevant hematologic toxicities and duration of the granulocyte nadir at the different dose levels. Neutropenia grade 3 and 4 occurred at all dose levels and in 87% of the courses. The percentages of courses with grade 3 and 4 neutropenia appeared to be docetaxel dose-dependent. Among patients treated according to schedule B (dose levels 6 to 8B), grade 4 neutropenia was documented in 94.5% to 100% of courses.

Infections were reported in 10% of all courses given, but were more common at the higher dose levels, starting from level 6A (13% to 23%). Neutropenia grade 4 associated with fever and hospital admission occurred in 4.5% of all courses, of which four courses were complicated with sepsis. Severe anemia was rare. Thrombocytopenia $\geq$ grade 2 only occurred during five courses at the higher dose levels.

Non hematologic toxicities

The most common non-hematologic toxicities are listed in Table 5. Nausea occurred in 5.5% of courses during the first 24 hours, later in 58.3% of courses, and overall in 61.3% (grade 3, 3.3%). Vomiting was

reported during the first 24 hours in 3.3% of courses, later in 38% of courses, and overall in 38.6% (grades 3 and 4, 2.5%). Diarrhea occurred in 38.3% (grade 3 and 4, 4.5%) of courses, while mucositis was reported in 26.3% and was severe (grade 3) in only two courses at dose levels 9 and 10A, respectively. Diarrhea was not related to dose or schedule. Alopecia was common and occurred at all dose levels in 88.8% of patients (grade 1, 22.2%; grade 2, 66.6%).

The docetaxel-cisplatin combination induced a predominantly sensory neuropathy in 29 (53%) of 55 assessable patients. At cumulative doses of both cisplatin and docetaxel above 200 mg/m^2, 26 of 35 patients (74%) developed a neuropathy, which was mild in 15, moderate in 10, and severe in one patient.

Significant correlations were observed between both the cumulative doses of docetaxel and cisplatin and the post-treatment sum score of neuropathy ($p<.01$), as well as the post-treatment VPT ($p<.01$). Nephrotoxicity grade 1 occurred in 28.7% of courses, while grade 2 was only documented in five courses (2.3%). Grade 2 creatinine increase occurred in one patient at dose level 6A after six courses, one patient at dose level 7B after six courses, two patients at dose level 10A after one course and five courses, respectively, and one patient at dose level 11 after one course.

Allergic reactions only occurred in 4.2% of courses. Skin toxicity was reported in 13.6% of courses and (mainly mild) nail toxicity in 39.6% of patients. Nail toxicity consisted of coloration, ridging, and sometimes onycholysis. Edema grade 1 (pitting edema without complaints) occurred in 23.4% of courses and grade 2 (pitting edema with complaints) in 4.5% of courses.

Overall, 12 patients discontinued treatment with the docetaxel-cisplatin combination because of non-hematologic toxicities, while six patients refused to continue.

TABLE III: RELEVANT HEMATOLOGIC TOXICITIES

	Dose level														
	1A	2A	3A	4A	5A	6A	6B	7A	7B	8A	8B	9A	10A	11A	Total (%)
No. of assessable patients	3	3	3	4	3 (+3)*	4(+2)	4(+2)	4(+5)	4(+1)	9	7	8(+1)	7	1	64
Courses assessable for hematologic toxicity	14	18	12	10	26	15	14	24	20	31	17	21	22	1	244
No. of courses with															
Grade 3 neutropenia	3	9	2	3	3	2	-	3	1	4	-	5	1	-	36 (15)
Grade 4 neutropenia	6	5	8	7	11	9	14	21	19	25	17	11	21	1	175 (72)
Febrile neutropenia	-	-	-	-	-	1	-	1	1	3	1	2	2	-	11 (4.5)
Grade 3 anemia	1	-	-	-	-	-	-	-	-	3	1	1	1	-	7 (3)
Grade 4 anemia	-	-	-	-	-	2	-	1	-	-	-	1	-	-	4 (2)
No. of patients with															
Grade 4 neutropenia	2	3	2	3	1(+1)*	4(+2)*	4(+2)*	4(+5)*	4(+1)*	9	7	5	6	1	

* Numbers in parentheses are patients initially treated at a higher dose level.

TABLE IV: DURATION OF GRANULOCYTE NADIR

	Dose level														
	1A	2A	3A	4A	5A	6A	6B	7A	7B	8A	8B	9A	10A	11A	Total
No. of evaluable courses administered	14	18	12	10	26	15	14	24	20	31	17	21	22	1	244
No. of courses with gr. 3 or 4 neutropenia	9	14	10	10	14	11	14	24	20	29	17	16	22	1	211 (87%)
No. of courses evaluable for nadir duration (*)	8	14	10	8	12	11	12	24	19	28	17	16	22	0	201 (82%)
Neutropenia: grade 3: median (range)	5(4-7)	7(4-7)	NA(7-10)	7(4-10)	4(3-6)	NA(2-7)	0	7(7-7)	NA(5-5)	6(3-7)	0	4(2-7)	NA(3-3)	NA	6(2-10)

Abbreviation: NA, not available.

* At least 1 blood count between day 2 and day 19, and 1 blood count within 7 days from nadir.

TABLE V: RELEVANT NON-HEMATOLOGIC TOXICITIES

	Dose level													
	1A	2A	3A	4A	5A	6A	6B	7A	7B	8A	8B	9A	10A	Total (%)
No. of assessable patients	3	3	3	4	3(+3)**	4(+2)	4(+2)	4(+5)	4(+1)	9	7	8(+1)	7	63
No. of assessable courses	14	18	12	10	26	15	14	24	20	31	17	21	22	243
No. of courses with:														
infections	-	1	2	-	-	1	-	4	3	5	4	2	3	25 (10.3)
severe asthenia	-	-	-	2	2	-	1	1	-	-	2	3	1	12 (4.9)
nausea ≤ gr 3	13	5	4	5	13	14	11	10	6	19	13	12	21	146 (60)
vomiting ≤ gr 3	8	3	2	1	5	8	7	3	3	14	13	8	16	91 (37.4)
mucositis ≤ gr 2	1	1	3	6	8	1	4	7	9	5	7	3	7	62 (25.5)
diarrhea ≤ gr 2	3	2	1	8	8	5	4	13	5	8	10	8	7	82 (33.7)
alopecia gr 1 + 2	3	3	2	4	3	3	3	4	4	8	5	7	7	56 (88.8)
skin toxicity	6	6	5	6	2	1	1	2	-	-	2	1	1	33 (13.6)
nail toxicity	-	2	1	2	-	1	2	4	4	1	3	2	3	25 (39.6)
allergic reactions	1	2	1	1	-	2	-	-	1	1	-	-	-	9 (3.7)
creatinin gr 1	2	2	1	2	5	4	11	5	8	9	2	7	4	62 (25.5)
neurotoxicity	1	3	1	4	1	1	2	2	2	5	3	4	3	32 (13.1)
edema gr 1+ 2	4	1	4	6	7	6	7	4	6	4	7	5	7	68 (28)

* Number of patients

** Numbers in parenthesas are patients initially treated at a higher dose level.

Toxicities that led to treatment discontinuation included neurotoxicity (one patient at dose level 8A and one at dose level 10A), nephrotoxicity (one patient at dose level 6A and one patient at dose level 7B), myocardial infarction (one patient at dose level 9), hemorrhagic colitis (one patient at dose level 8A), edema and weight gain (one patient at dose level 7B), and anorexia combined with weight loss, dehydration and electrolyte disturbances (three patients, respectively, at dose level 7A, 8B and 10A). The myocardial infarction was not related to the docetaxel-cisplatin combination, but was a reason to discontinue treatment.

Dose limiting toxicities

Dose-limiting toxicities observed throughout the study are listed in Table 6. Grade 4 neutropenia that lasted more than 7 days occurred mainly in patients who had received prior chemotherapy.
Two patients developed a long-lasting neutropenia grade 4 after the first course, while in four patients this toxicity was reported after the third course. Fever associated with grade 4 neutropenia occurred in 4.5% of all courses and was more common at the higher dose levels. Severe diarrhea was rare and did not appear to be dose-dependent, while grade 3 mucositis and nausea/vomiting $\geq$ grade 3 mainly were reported at the higher dose levels. Renal toxicity grade 2 and neurotoxicity grade 3 were rarely observed at the higher dose levels.

Pharmacology

The pharmacokinetics of cisplatin and docetaxel were determined in patients treated according to schedule A (47 patients) and schedule B (14 patients). There were no significant differences in pharmacokinetic parameters between the two groups. The most relevant data are listed in Table 7. Docetaxel protein-binding was high (96%) and not influenced by cisplatin.

TABLE VI: SEVERE HEMATOLOGIC AND NON HEMATOLOGIC TOXICITIES

	Dose level													
	1A	2A	3A	4A	5A	6A	6B	7A	7B	8A	8B	9A	10A	Total (%)
No. of assessable patients	3	3	3	4	3(+3*)	4(+2)	4(+2)	4(+5)	4(+1)	9	7	8(+1)	7	63
No. of assessable courses	14	18	12	10	26	15	14	24	20	31	17	21	22	243
No. of courses with:														
- grade 4 neutropenia > 7 days	3	-	-	1	2	3	2	2	-	-	1	1	-	15 (6.2)
- grade 4 neutropenia with fever	-	-	-	-	-	1	-	1	1	3	1	2	2	11 (4.5)
- grade 4 platelets	-	-	-	-	-	-	-	-	-	-	-	-	-	0 (0)
- grade 3/4 diarrhea	-	2	1	1	1	-	1	-	-	3	1	-	1	11 (4.5)
- grade 3 stomatitis	-	-	-	-	-	-	-	-	-	-	-	1	1	2 (0.8)
- grade 3/4 nausea/vomiting	-	-	-	-	-	1	-	1	-	2	1	1	1	6 (2.5)
- creatinine grade 2	-	-	-	-	-	1	-	-	1	-	-	-	2	4 (1.6)
- neurotoxicity grade 3	-	-	-	-	-	-	-	-	-	-	-	-	1	1 (0.4)

Numbers in parentheses are patients initially treated at a higher dose level.

TABLE VII: PHARMACOKINETIC PARAMETERS OF DOCETAXEL AND CISPLATIN

		docetaxel (LT)		cisplatin (C)	
		Clearance (l/h/m^2)	V_{ss} (l/m^2)	Clearance (l/h/m^2)	V_{ss} (l/m^2)
schedule A (T→C)	median	21.52	56.20	19.05	0.21
	range	(11.15 - 38.98)	(8 - 249)	(13.10 - 31.30)	(0.12 - 0.38)
	N	43	37	47	47
schedule B (C→T)	median	22.56	71.90	19.24	13.37
	range	(6.08 - 45.18)	(19 - 256)	(14.12 - 33.62)	(8.5 - 24.22)
	N	14	13	14	14

NOTE. Not significantly different.
Abbreviation: V_{ss}, volume at steady-state.
* Clearance = total-body clearance; clearance of cisplatin is based on unbound platinum.

Responses

One complete response (CR) was achieved in a 70-year-old patient with an urothelial cell carcinoma. Partial responses (PRs) were documented in head and neck cancer (two of five patients), colorectal cancer (one of twenty-two patients), stomach cancer (one of five patients), carcinoma of unknown primary (four of thirteen patients), and Ewing's sarcoma (one of two patients).

DISCUSSION

Cisplatin is one of the most frequently applied drugs for the treatment of patients with solid tumors. It is active in a wide variety of these tumors and the side effects that hampered its use shortly after its introduction into the clinic have now largely been overcome by supportive measures such as hyperhydration and the coadministration of the $5HT_3$ antagonists as antiemetics. Docetaxel was first synthesized in 1986 and entered clinical studies as recent as the early 1990s. Nevertheless, just a few years later, the drug was identified as having activity in a wide variety of solid tumors (14-26). Because of the only partly overlapping toxicity profiles and their widespread activity against solid tumors, it was considered worthwhile to pursue a combination regimen with these drugs.

The presently reported phase I study was performed to assess the feasibility of the combination and to determine the MTD and the side effects with an emphasis on sequence-dependent effects. The importance of the latter has only recently been identified to be of potential relevance (32) and sequence investigations should become an integral part of all phase I studies that involve combinations of drugs. Moreover, preclinical studies had revealed that specific intervals in the sequencing of both drugs did lead to optimal efficacy (M. Bissery, personal communication; Rhône-Poulenc Rorer, data on file). In the present study, two sequences were studied, both of which were considered as having optimal efficacy in the preclinical studies.

It appeared feasible to combine docetaxel and cisplatin at their usual single-agent doses. Because the single patient entered at the dose of 100

mg/m^2 of both docetaxel and cisplatin died already after 3 days due to neutropenic sepsis and it was considered unlikely that the combination would ever be given in multicenter trials at such high doses, this dose level was not further tested, even though formally according to protocol, dose-limiting toxicity was never reached. The major toxicity of the combination of docetaxel and cisplatin as observed in the present study was granulocytopenia, which was severe in the majority of courses (grade 3 and 4, 87%) at all dose levels. It appeared to be docetaxel dose- dependent at the lower dose levels and was ubiquitous at the higher dose levels. Significant sigmoid relationships have been established between the magnitude of exposure (area under the curve [AUC]) of docetaxel and leukocytopenia and thrombocytopenia (Ma *et al.*, submitted). There were no significant differences in hematologic toxicities between schedules A and B, although there appeared to be a trend toward a higher incidence of grade 3 and 4 leukocytopenia in schedule B ($p = .09$). Similar observations were made in a phase I study that combined paclitaxel and cisplatin, in which neutropenia grade 4 occurred more often when cisplatin preceded paclitaxel (32). Infections and neutropenia grade 4 associated with fever occurred only in 10% and 4.5% of courses, respectively, and were more common at the higher dose levels. This relatively low percentage, if balanced against the severity of granulocytopenia, reflects the short duration of the granulocytopenia. The duration of granulocytopenia as listed in Table 4 is similar to the duration of granulocytopenia that results from single-agent docetaxel treatment.

The most common non-hematologic toxicities were nausea, vomiting, diarrhea and mucositis, most of them being mild to moderate. There were no significant differences in the occurrence of non-hematological toxicities between schedules A and B. Nausea and vomiting occurred predominantly after 24 hours from drug administration, while acute nausea and vomiting were rare. Some patients developed severe diarrhea with bloody stools. Endoscopic examination of two of these patients showed a diffuse sigmoiditis with intramucosal bleedings. Pathologic examination showed destruction of the epithelial surface, bleedings, edema and dilated capillaries. Also, after treatment

with paclitaxel given as a 24-hour continuous infusion, epithelial necrosis in the gastrointestinal tract (from oesophagus to colon) was described in two patients 1 day after treatment with paclitaxel. This necrosis was associated with the typical features of paclitaxel toxicity, which consist of polymerized microtubule accumulation and mitotic arrest (33).

In 53% of 55 assessable patients, the docetaxel-cisplatin combination induced a predominantly sensory neuropathy. At cumulative doses of both docetaxel and cisplatin above 200 mg/m^2, 26 of 35 patients developed a neuropathy, which was mild in 15, moderate in 10 and severe in one patient. This last patient, who was pretreated with chemotherapy, developed a severe neuropathy after five courses of chemotherapy at dose level 10A. Significant correlations were observed between both the cumulative doses of docetaxel and cisplatin and the posttreatment sum score of neuropathy ($p < .01$), as well as the post-treatment VPT ($p < .01$). The neurotoxic effects of both agents used in combination seem more severe than with the use of either docetaxel or cisplatin as single agents at comparable doses. In a phase I study on the combination of paclitaxel and cisplatin, (32) it was also suggested that these agents act synergistically in producing neurotoxicity. The incidence of neurotoxic manifestations was disproportionately greater than that reported with either paclitaxel or cisplatin alone at comparable single and cumulative doses.

The incidence of docetaxel-specific toxicities like hypersensitivity reactions, nail and skin toxicity, and edema was relatively low and did not constitute a major clinical problem. In this study, the majority of patients received premedication that consisted of dexamethasone and clemastine fumarate, which might account for the low incidence of the aforementioned side effects. The incidence of these side effects seems much higher if docetaxel is given as a single agent without such premedication (34).

The pharmacokinetics of non-protein-bound cisplatin and docetaxel were determined in both treatment schedules. There were no significant differences in pharmacokinetic parameters of cisplatin and docetaxel between schedules A and B. The pharmacokinetic results for docetaxel were similar to those

observed after administration of docetaxel as a single agent. There did not appear to be a pharmacokinetic interaction between docetaxel and cisplatin. However, in a phase I study that combined paclitaxel and cisplatin, concurrent pharmacologic studies demonstrated that the treatment sequence of cisplatin followed by paclitaxel was associated with a 25% lower clearance rate of paclitaxel. The pharmacologic exposure to paclitaxel, the principal myelotoxic agent in the combination, was 33% higher when cisplatin was administered before paclitaxel, which was the most toxic sequence (32). The interval between cisplatin and docetaxel administration on schedule B was 21 hours, while the interval between cisplatin and paclitaxel administration was only 6 hours (32). This difference in scheduling might account for the difference in pharmacokinetic interaction between the two combinations.

Antitumor responses to the combination of docetaxel and cisplatin were seen in a variety of tumor types. Remarkable was the CR in one patient with urothelial cell carcinoma. The combination of these drugs also appeared to be active in carcinoma of unknown primary and head and neck cancer. A phase II study on the combination of docetaxel and cisplatin is now being performed in patients with head and neck cancer.

Based on the experience obtained in this phase I study, we recommend that phase II studies use the sequence of docetaxel given before cisplatin, since this is more convenient. Although considerable side effects will have to be expected, repeated cycles of 100 mg/m^2 of docetaxel with 75 mg/m^2 of cisplatin (dose level 8A) or 85 mg/m^2 of docetaxel with 100 mg/m^2 of cisplatin (dose level 10A) appear feasible, especially in patients with a good physical condition. At dose level 8A, 81% of the cycles could be given at full dose, with a median cumulative dose of 495 mg/m^2 (range, 184 to 593) for docetaxel and of 366 mg/m^2 (range, 150 to 448) for cisplatin. The median relative dose-intensity of docetaxel and cisplatin, which reflects the dose actually received and delay between treatment administration, was 0.98 (range, 0.92 to 1.01) and 1.00 (range, 0.95 to 1.03), respectively. At dose level 10A 88% of cycles could be given at full dose, with a median cumulative dose of 171 mg/m^2 (range, 84 to 511) for docetaxel and of 200 mg/m^2 (range,

98-596) for cisplatin. The median relative dose-intensity of docetaxel and cisplatin was 0.97 (range, 0.88 to 1.05) and 0.97 (range, 0.76 to 1.01), respectively. Proper patient selection based on performance score will be of utmost importance in phase II studies that apply these doses.

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PERIPHERAL NEUROPATHY INDUCED BY COMBINATION CHEMOTHERAPY OF DOCETAXEL AND CISPLATIN

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SUMMARY

Docetaxel, a new semisynthetic taxoid that has demonstrated promising activity as an antineoplastic agent, was administered in combination with cisplatin to sixty-three patients in a dose-escalating study. As both drugs were known to be potentially neurotoxic, peripheral neurotoxicity was prospectively assessed in detail. Neuropathy was evaluated by clinical sum-score for signs and symptoms and by measurement of the Vibration Perception Threshold (VPT). The severity of neuropathy was graded according to the National Cancer Institute's "Common Toxicity Criteria". The docetaxel-cisplatin combination chemotherapy induced a predominantly sensory neuropathy in twenty-nine (53%) out of fifty-five evaluable patients. At cumulative doses of both cisplatin and docetaxel above 200 mg/m^2, twenty-six (74%) out of thirty-five patients developed a neuropathy which was mild in fifteen, moderate in ten and severe in one patient. Significant correlations were present between both the cumulative dose of docetaxel and cisplatin and the post-treatment sum-score of neuropathy ($p < 0.01$) as well as the post-treatment VPT ($p < 0.01$). The neurotoxic effects of this combination were more severe than either cisplatin or docetaxel as single agent at similar doses.

INTRODUCTION

Docetaxel (Taxotere) is a new semisynthetic taxoid that has demonstrated substantial clinical activity against a wide variety of solid tumors (1-7). Docetaxel inhibits tubulin depolymerization and promotes microtubule assembly, resulting in dysfunctional microtubules (1).

In view of their partly non-overlapping side-effects and their activities in a wide range of tumor types, developing combination chemotherapy regimens, including both taxoid and platins, is of major interest (8-10). An important dose-dependent side-effect of cisplatin is the development of peripheral neuropathy, mainly affecting thick-fiber-mediated sensory qualities (11-15). Neuropathy has also been reported as a dose-dependent side-effect of

treatment with paclitaxel (Taxol). (16, 17). As expected, trials on combination chemotherapy of cisplatin and paclitaxel found a high incidence of peripheral neuropathy (8-10).

Peripheral neurotoxicity has been reported as a frequent, but usually mild side-effect of docetaxel in several phase I and phase II studies (2-7, 18-21). The neurotoxic effects of docetaxel in combination chemotherapy with cisplatin are unknown. In our institution a phase I trial on the combination of docetaxel and cisplatin in metastatic or locally advanced solid tumors was conducted (22). In order to study the neurotoxicity of this combination chemotherapy, we prospectively evaluated all patients participating to this trial by detailed neurological examinations.

PATIENTS AND METHODS

All participating patients had a metastatic or locally advanced solid tumor for which no other appropriate anti-tumor therapy was available. Other inclusion criteria included age 18-75 years, WHO performance status 0-2, no prior treatment with platinum derivates or taxoids, normal organ functions, a life expectancy of 3 months or more and written informed consent. Patients with symptomatic peripheral neuropathy grade 1 or more according to the "National Cancer Institute (NCI) criteria" (Table I) and patients with brain or leptomeningeal metastases were excluded. Chemotherapy was administered in 3-weekly regimens. Docetaxel, supplied by Rhône-Poulenc Rorer, was given as a 1-hour infusion. Cisplatin was dissolved in 3% saline and administered as a 3-hour infusion with 24 hours hyperhydration. In most patients, docetaxel was given 3 hours before cisplatin. In some patients, the sequence was reversed and docetaxel was given 18 hours following cisplatin administration. Scheduled dose-escalation included cisplatin doses of 50, 75 and 100 mg/m^2 and docetaxel doses of 55, 70, 85 and 100 mg/m^2.

TABLE I: SEVERITY OF PARESTHESIAS AND "COMMON TOXICITY CRITERIA" OF THE NCI

PARESTHESIAS	CTC-NEUROSENSORY
0 = no	0 = no symptoms or signs
1 = temporary	1 = mild paresthesias, loss of deep tendon reflexes
2 = continuous light	2 = moderate paresthesias, objective sensory loss
3 = severe	3 = severe paresthesias, sensory loss interfering with function
4 = unbearable	

No other neurotoxic drugs were applied during the trial or follow-up period.

The severity of neuropathy was assessed by a questionnaire for neurological symptoms using standardized neurological examination and measurements of the Vibration Perception Threshold (VPT) before the start of treatment, after each cycle, at 2 weeks after the last dose of docetaxel and every 3 months thereafter. The questionnaire established separately absence (0) or presence (1) of paresthesias, numbness, loss of dexterity and unsteadiness of gait. On sensory examination, position sense, vibration sense, pin-prick sensation, Romberg's sign, Romberg's sign with heel-to-toe stand and tendon reflexes of the legs were each scored as normal (0) or abnormal (1). A sum-score for these signs and symptoms was calculated (minimum 0, maximum 11). The severity of paresthesias was graded on a 5-point scale (Table I). Sensory loss was defined as an abnormal test on either position sense, vibration sense or pin-prick sense. Patients were asked whether they experienced Lhermitte's sign or pain. Distal muscle strength in the lower extremities was tested. Motor signs were defined as the presence of objective weakness. The severity of neuropathy was scored according to the NCI Common Toxicity Criteria (CTC) for sensory neuropathy (Table I). VPT was measured at the dorsum of the second metacarpal bone of the left hand with a Vibrameter type IV (Somedic AB, Stockholm, Sweden) and recorded in micrometers (μm) of skin displacement. This Vibrameter uses a vibratory

frequency of 100 Hz and corrects for pressure-induced alterations of vibratory amplitude. The method of limits was used to obtain the mean VPT, and this was repeated three times (23). The VPT has been shown to be a reliable technique to monitor cisplatin neuropathy and shows a good correlation with the sum-score of neuropathic signs and symptoms as observed previously (24-26). It has also been applied to quantify paclitaxel-induced neuropathy (17).

In some patients electrophysiological studies were carried out before and after treatment. Distal latency and nerve conduction velocity (NCV) of the ulnar (sensory and motor), peroneal (motor) and sural nerve, compound motor action potential (CMAP) of the ulnar and peroneal nerve and sensory nerve action potential (SNAP) of ulnar and sural nerve were determined. A 50% decrease in CMAP and SNAP amplitude and a 15% decrease of NCV were considered abnormal.

The first post-treatment evaluation was used as primary endpoint for the assessment of neurotoxicity. Cycles of docetaxel and cisplatin given after the last neurological evaluation, which occurred in eight patients, were not counted in the analysis and excluded from the calculation of the cumulative dose.

A subdivision was made into three groups according to cumulative dose of cisplatin and docetaxel. The mean increase in sum-score and the ratio of VPT post-treatment to VPT pretreatment (VPT post-pre ratio) within groups were calculated. A comparison of the severity of neuropathy in relation to cumulative dose was made with two other prospective trials performed in our institution in the same period (15, 20). In these trials cisplatin and docetaxel were studied as single chemotherapeutic agents, and identical methods for measurement of neuropathy were applied as described here.

The incidence of neurological signs and symptoms at the first evaluation after the last cycle was determined. Patients with pre-existing signs or symptoms were not included in these calculations. Graded paresthesias pre-treatment were included only if there was an increase in the grade of paresthesias post-treatment. The change in sensory sum-score and the VPT post-pre ratio were calculated for each patient. Spearman rank-correlations were calculated to describe the strength of the association between cumulative

doses of cisplatin and docetaxel and the increase in sensory sum-score and the VPT post-pre ratio. Because of the skewed distribution of the VPT, the geometric mean was used to determine the mean of the VPT post-pre ratio. For the sensory sum-score, the arithmetic mean was calculated.

RESULTS

Sixty-three patients were entered into the trial. Eight of these sixty-three patients were excluded for assessment of neurotoxicity because of lack of pre-treatment evaluation.

Patient characteristics, tumor type and previous chemotherapy of fifty-five patients evaluable for the present analysis are shown in table II.

TABLE II: PATIENT CHARACTERISTICS AND TUMOR TYPE

Number of evaluable patients	55
Sex male/female	26/29
Age mean	53
(range)	(21-74)
Tumor type	
Colorectal	23
ACUP[1]	14
Breast	5
Head and neck	3
Sarcoma	2
Melanoma	2
NSCLC[2]	2
Miscellaneous	4
Prior therapy	
cisplatin	-
vincristine	1
other chemotherapy	27

[1]) Adenocarcinoma of unknown primary
[2]) Non-small cell lung carcinoma

Twenty-seven patients had previously been treated with non-neurotoxic chemotherapy. One patient had been treated with Vincristine. None of the patients had received prior treatment with cisplatin. Five patients had diabetes mellitus and five patients reported alcohol abuse.

Twenty patients received 1 or 2 cycles, six patients 3 to 4 cycles, twenty-eight patients 5 to 6 cycles and one patient 8 cycles before their last evaluation. The mean dose per cycle of cisplatin was 74 mg/m^2 (range 50-100 mg/m^2) and of docetaxel 82 mg/m^2 (range 38-100). The mean given cumulative dose of cisplatin was 297 mg/m^2 (range 75-600 mg/m^2) and of docetaxel 326 mg/m^2 (range 75-600 mg/m^2). The mean duration of follow-up after the last cycle was 96 days (range 7-315 days).

Table III shows the incidence of neuropathic signs and symptoms at the first post-treatment evaluation. Paresthesias were seen in 24 patients (44%) in both hands and feet (n = 18) or in the feet only (n = 6). Three patients suffered from pain in either hands or feet, which was felt to be secondary to the neuropathy.

Table IV shows the mean increase in sensory sum-score, the mean VPT post-pre ratio, the severity of paresthesias and the CTC-neurosensory grade at first post-treatment evaluation, classified by cumulative dose of docetaxel and cisplatin. According to CTC criteria, twenty-nine patients developed a sensory neuropathy. In the group with a cumulative dose of both cisplatin and docetaxel below 200 mg/m^2 three out of twenty patients showed a mild sensory neuropathy (grade 1).

Out of 16 patients treated with a cumulative dose docetaxel above 200 mg/m^2 and cisplatin between 200 and 400 mg/m^2, 12 patients developed a sensory neuropathy which was mild in 7 patients (grade 1) and moderate in 5 patients (grade 2). In the group with cumulative dose of cisplatin above 400 mg/m^2 and docetaxel above 200 mg/m^2, 14 out of 19 patients developed a sensory neuropathy, grade 1 in eight, grade 2 in five and grade 3 in 1 patient. In 4 patients, treatment had to be discontinued because of neurotoxicity.

Twenty-three patients had two or more post-treatment evaluations. Two of these patients developed a mild neuropathy (grade 1) during follow-up.

TABLE III: NEUROPATHIC SIGNS AND SYMPTOMS AT FIRST POST-TREATMENT EVALUATION

	N	(%)
Paresthesias	24/55	(44)
grade 1	8[1]	
grade 2	9[2]	
grade 3	5[3]	
grade 4	2	
Pain	3/54[4]	(6)
Numbness	17/53	(32)
Loss of dexterity	14/53	(26)
Unsteadiness of gait	9/53	(17)
Lhermitte's sign	7/54	(13)
Sensory loss	19/46	(41)
Motor signs	9/54	(17)
Romberg's sign	2/51	(4)
Loss of knee jerks	23/55	(42)
Loss of ankle jerks	29/45	(64)

[1]) Excluding one patient with pre-existing paresthesias grade 1
[2]) Including one patient with pre-existing paresthesias grade 1
[3]) Including one patient with pre-existing paresthesias grade 2
[4]) Patients with these signs or symptoms at pre-treatment evaluation or with missing data are excluded

In 4 patients neuropathy further deteriorated during follow-up: 1 patient developed a moderate neuropathy (grade 2) and 3 patients a severe (grade 3) neuropathy.

In 43 patients, the sequence of administration was docetaxel before cisplatin and in 12 patients vice versa. There was no difference in the severity of neurotoxicity as measured with the sensory sum-scores between these two different regimens.

We found a clear correlation between the increase in VPT and the increase in sum-score (r_s = 0.34, p = 0.02) following treatment.

TABLE IV: SEVERITY OF NEUROPATHY IN RELATION TO CUMULATIVE DOSE OF DOCETAXEL AND CISPLATIN

cisplatin docetaxel	< 200 mg/m^2 < 200 mg/m^2 N = 20	200-400 mg/m^2 > 200 mg/m^2 N = 16	>400 mg/m^2 >200 mg/m^2 N = 19
Sensory sum-score increase mean (± s.d.)[1]	1.1 ± 1.2	4.3 ± 2.4	3.5 ± 2.9
VPT post-pre ratio mean (± s.d.)[2]	1.2 ± 0.7	1.9 ± 0.9	4.3 ± 4.0
Paresthesias[3]			
grade 1	1(1)[4]	2(2)	5(3)
grade 2	1(1)	5(4)	3(7)
grade 3	-	2(3)	3(3)
grade 4	-	2(2)	-(1)
CTC neurosensory[3]			
grade 1	3(2)	7(7)	8(10)
grade 2	-(1)	5(4)	5(3)
grade 3	-	-(1)	1(3)

[1]) difference between first post-treatment and pre-treatment score.
[2]) difference between first post-treatment and pre-treatment score, divided by the pre-treatment score (post-pre ratio).
[3]) incidence at first post-treatment evaluation.
[4]) Numbers in parentheses indicate when maximum scores post-treatment are considered.

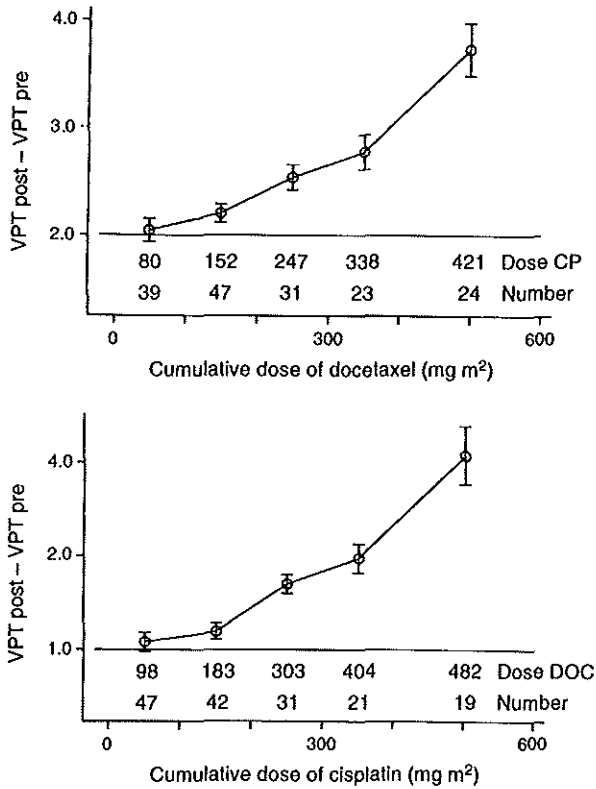
Both the cumulative doses of docetaxel and cisplatin showed a statistically significant correlation with the increase in sum-score (r_s = 0.44 and 0.39 respectively, $p < 0.01$) and the change in VPT (r_s = 0.68 and 0.65 respectively, $p < 0.001$).

Figure 1 shows the VPT post-pre ratio in relation to cumulative dose of docetaxel and cisplatin. Figure 2 shows the relation of cumulative doses of these drugs and change in sensory sum-score.

Electrophysiological studies before and after treatment were carried out in 26 patients. It showed a decrease in SNAP amplitudes in 15 patients, a decrease in CMAP amplitudes in 1 patient and both a decrease in SNAP and CMAP amplitudes in 4 patients. The NCV studies were unchanged in 6 patients, most of whom had been treated with low cumulative doses of both

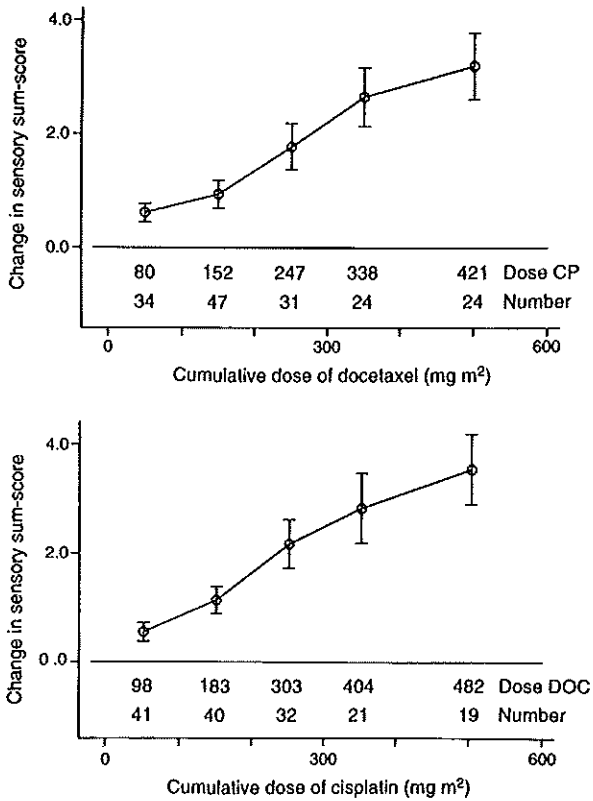
cisplatin and docetaxel. The cumulative dose in the 4 patients with both motor and sensory involvement was similar to the cumulative dose of patients with only sensory involvement.

FIGURE 1



The mean change (± s.e.) in vibration perception threshold (VPT) post-treatment in relation to the cumulative dose of docetaxel and cisplatin (mg/m^2). The figures above the horizontal axis indicate the number of patients evaluated and the mean dose of cisplatin (CP) and docetaxel (DOC) in each dose subgroup.

FIGURE 2



The mean change (± s.e.) in sensory sum-score post-treatment in relation to the cumulative dose of docetaxel and cisplatin (mg/m²). The figures above the horizontal axis indicate the number of patients evaluated and the mean dose of cisplatin (CP) and docetaxel (DOC) in each dose subgroup.

TABLE V: COMPARISON OF THE SEVERITY OF NEUROPATHY BETWEEN PATIENTS TREATED WITH DOCETAXEL ALONE (HILKENS, 1996) AND PATIENTS TREATED WITH DOCETAXEL-CISPLATIN COMBINATION CHEMOTHERAPY, IN RELATION TO THE CUMULATIVE DOSE DOCETAXEL

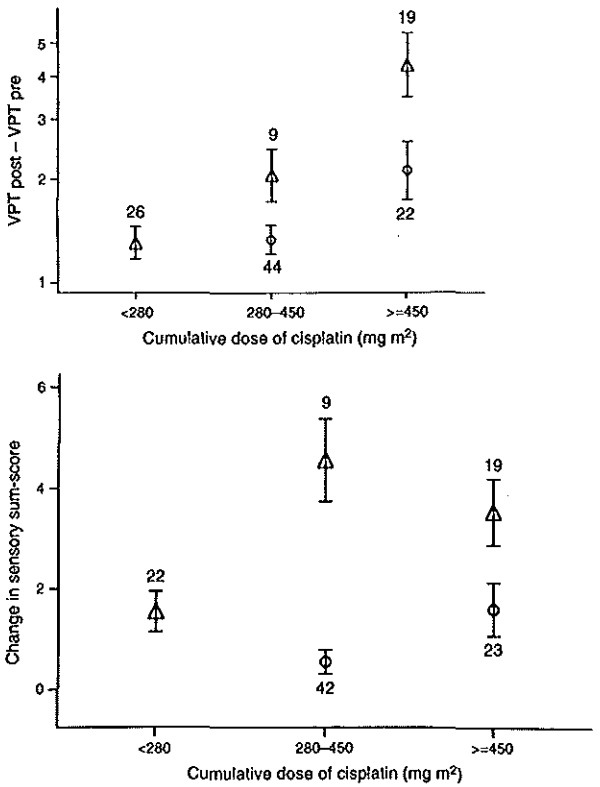
	docetaxel < 300 mg/m²		docetaxel 300-600 mg/m²	
	without cisplatin	with cisplatin	without cisplatin	with cisplatin
N	14	24	12	31
Cumulative dose of cisplatin (mean ± s.d.) (mg/m²)	-	157 ±65	-	406 ±110
Sensory sum-score increase (mean ± s.d.)[1]	1.5 ±1.2	1.5 ±1.7	2.9 ±2.5	3.9 ±2.7
VPT post-pre ratio (mean ± s.d.)[2]	1.4 ±0.9	1.2 ±0.7	1.1 ±0.4	3.3 ±2.7
Paresthesias[3]				
grade 1	5	1	3	7
grade 2	1	1	3	8
grade 3	-	1	-	4
grade 4	-	1	-	1
CTC neurosensory[3]				
grade 1	2	3	7	15
grade 2	-	2	-	8
grade 3	-	-	-	1

[1]) difference between first post-treatment and pre-treatment score.
[2]) difference between first post-treatment and pre-treatment score, divided by pre-treatment score (pre-post ratio).
[3]) incidence at first post-treatment evaluation.

Table V shows a comparison of the severity of neuropathy in relation to cumulative dose docetaxel between patients in the combination chemotherapy trial and patients treated with docetaxel alone in another prospective trial conducted in our institution (20). At low cumulative doses docetaxel (and consequently also low doses of cisplatin in the combination chemotherapy trial), there is a low incidence of neuropathy in both trials.

When patients with cumulative doses of docetaxel above 300 mg/m^2 are considered, a higher incidence and more severe neuropathy is found in patients treated with combination chemotherapy than in patients treated with docetaxel alone.

FIGURE 3



The mean change (± s.e.) in Vibration Perception Threshold (VPT) and sensory sum-score post-treatment in relation to the cumulative dose of cisplatin (mg/m^2). ▵, Patients treated with docetaxel-cisplatin combination; ○, patients treated with cisplatin alone (Hilkens *et al.*, 1994) The figures indicate the number of patients evaluated.

Figure 3 compares the relative change in VPT and the change in sensory sum-score in relation to the cumulative dose of cisplatin between patients from this trial and patients treated with cisplatin alone (15). It shows a more severe neuropathy in the patients treated with the combination chemotherapy regimen, particularly at higher cumulative doses of cisplatin.

DISCUSSION

In recent years, docetaxel has appeared to be one of the most active new antineoplastic agents. Peripheral neuropathy is one of the potentially dose-limiting side-effects. In several phase II trials on docetaxel, a mild to moderate, mainly sensory, neuropathy was observed (2-7, 20, 21, 27). In a study of 41 patients treated with single-agent docetaxel (100 mg/m^2 every 3 weeks; cumulative doses 200-1100 mg/m^2) 49% of the patients developed a usually mild neuropathy (20). The neuropathy appeared to be dose dependent and caused severe and disabling neuropathy in some patients at higher dose levels. Severe motor involvement occurred in two of these patients.

In trials on combination chemotherapy of cisplatin with another taxoid, paclitaxel, a high incidence of neuropathy was found. In a phase I study of paclitaxel (110-200 mg/m^2 per cycle) and cisplatin (50-75 mg/m^2 per cycle) in 44 patients (median number of cycles 3; range 1-12), 27% developed a mild to moderate neuropathy (8). The incidence of neuropathy was disproportionately higher than expected with either paclitaxel or cisplatin alone at similar single and cumulative doses. In a study of 32 patients treated with higher doses paclitaxel (135-350 mg/m^2 per cycle) and cisplatin (75-100 mg/m^2 per cycle) 75% developed a neuropathy (29). It was suggested that the neuropathy was mainly due to paclitaxel.

The severity of the neuropathy was related to both the cumulative and single dose of paclitaxel and the presence of a pre-existing medical disorder associated with neuropathy (diabetes, alcoholism). The neuropathy was of axonal nature with predominantly sensory signs, although electrophysiological studies established the additional involvement of motor nerves (10).

To date, there are no results of studies on docetaxel-cisplatin combination chemotherapy regimens. In the present study, we observed that 53% of patients treated with docetaxel and cisplatin, in a wide range of cumulative doses, developed a mainly sensory neuropathy. When only patients with cumulative doses of docetaxel and cisplatin above 200 mg/m^2 were considered, 71% developed a neuropathy. At higher dose levels, some patients showed moderate or severe neuropathy. Nine of these patients had motor signs. In five out of twenty-six patients in whom neurophysiological studies were performed, motor involvement was found. Neuropathy was the dose-limiting side-effect in four patients.

We were able to compare the results of this trial with two other trials performed in our institution in which patients were treated with either docetaxel or cisplatin as single agent (15, 20). As expected, the combination of these two neurotoxic agents tends to induce a more severe neuropathy then either of the two drugs alone. However, since these single- and combination chemotherapy schedules were not studied in a comparative trial this should be interpreted with caution. As the cumulative dose cisplatin and the cumulative dose of docetaxel were closely related in our study, we could not detect which drug accounted for most of the neuropathy. A synergistic effect of the two drugs cannot be excluded.

The value of the VPT as a sensitive indicator of neuropathy in this study is not unequivocal. Several reports have demonstrated that VPT is a reliable measure of cisplatin neuropathy (24-26). In a previous study, we did not establish a significant relation between VPT and the severity of docetaxel-induced neuropathy, possibly because small fibre functions are compromised in this neuropathy (20). The change in VPT, in this study, can probably be accounted for by cisplatin which mainly affects large myelinated fibres.

In a phase I study on paclitaxel-cisplatin combination chemotherapy, it was suggested that the sequence of cisplatin administration before paclitaxel may be related to more profound neutropenia (8). We were unable to detect differences in the severity of neurotoxicity in relation to the sequence of administration of cisplatin and docetaxel. As only twelve patients received

cisplatin before docetaxel, no firm conclusions can be drawn.

In conclusion, the combination chemotherapy of docetaxel and cisplatin induces a dose-dependent sensory neuropathy. At higher dose range, neuropathy is encountered in a relatively high proportion of patients. With cumulative doses of both cisplatin and docetaxel between 200 and 600 mg/m^2, one third of the patients developed a moderate or severe neuropathy. The severity of neuropathy is higher than with the use of either cisplatin or docetaxel as a single agent at similar doses. Further study on the possible attenuating effects of neuroprotective agents such as WR-2721 (amifostine) (28-30), glutathione (31, 32) and nerve growth factor (33, 34) is warranted.

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PHASE I STUDY ON DOCETAXEL AND IFOSFAMIDE IN PATIENTS WITH ADVANCED SOLID TUMORS

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SUMMARY

Docetaxel and ifosfamide have shown significant activity against a variety of solid tumors. This prompted a phase I trial on the combination of these drugs. This phase I study was performed to assess the feasibility of the combination, to determine the maximum tolerated dose (MTD) and the side effects, and to propose a safe schedule for further phase II studies. A total of 34 patients with a histologically confirmed solid tumor, who were not pretreated with taxanes or ifosfamide and who had received no more than one line of chemotherapy for advanced disease were entered. Treatment consisted of docetaxel given as a 1 hour infusion followed by ifosfamide as a 24 hour infusion (schedule A), or ifosfamide followed by docetaxel (schedule B) every 3 weeks. Docetaxel doses ranged from 60-85 mg/m^2 and ifosfamide doses from 2.5-5.0 g/m^2. Granulocytopenia grade 3 and 4 were common (89%), short lasting and ifosfamide dose dependent. Febrile neutropenia and sepsis occurred in 17% and 2% of courses respectively. Non-hematologic toxicities were mild to moderate and included alopecia, nausea, vomiting, mucositis, diarrhea, sensory neuropathy, skin- and nail toxicity and edema. There did not appear to be any pharmacokinetic interaction between docetaxel and ifosfamide. One complete response (CR) (soft tissue sarcoma) and 2 partial responses (PRs) were documented. A dose of 75 mg/m^2 of docetaxel combined with 5.0 g/m^2 of ifosfamide appeared to be manageable. Schedule A was advocated for further treatment.

INTRODUCTION

Docetaxel is a new antimicrotubule agent that enhances polymerization of tubulin into stable microtubules and inhibits microtubule depolymerization. This induces a disruption of the equilibrium within the microtubule system and ultimately leads to cell death (1-3). Docetaxel has been studied in many murine tumor models, showing activity against subcutaneous (s.c.) B16 melanoma, MX-1 mammary cancer, C38 colon carcinoma, CX-1 colon carcinoma, LX-1

lung carcinoma, s.c. early stage pancreatic ductal adenocarcinoma (PO_3), s.c. colon adenocarcinoma 51 (C51), SK MEL-2 melanoma and OVCAR-3, HOC 8, HOC 10 and HOC 22 ovarian carcinomas (4-7). In phase I studies on single agent docetaxel the major dose limiting toxicity (DLT) was neutropenia that appeared to be short-lasting, dose-dependent, schedule-independent and non-cumulative (8-13). Based on these phase I studies the recommended single agent dose and schedule for docetaxel was 100 mg/m^2 given as a 1-hour infusion every 3 weeks. Phase II studies on docetaxel showed activity in breast cancer (14-18), non-small cell lung cancer (19-21), head- and neck cancer (22), gastric cancer (23), melanoma (24), soft tissue sarcoma (25) and pancreatic cancer (26). The most important side-effect was an early and short-lasting neutropenia which in 20% of the patients was complicated by infection (27). Alopecia was a common side-effect and usually universal. Gastrointestinal side-effects like nausea, vomiting, diarrhea and mucositis were mild and easily treated. Other side-effects included asthenia, infrequent hypersensitivity reactions, skin reactions, nail changes, mild sensory neuropathy and fluid retention. The application of premedication consisting of corticosteroids has markedly reduced the incidence of hypersensitivity reactions (28) and seems to decrease the severity of fluid retention (29). Therefore most studies on docetaxel are now performed with standard corticosteroid premedication.

Ifosfamide is an alkylating drug that among others has shown to be active against non-small cell lung cancer (30), testicular cancer (31), breast cancer (32) and soft tissue sarcoma (33). The main side-effects of ifosfamide consist of urotoxicity nephrotoxicity, neurotoxicity, myelosuppression, nausea, vomiting and alopecia. Ifosfamide can be administered orally or intravenously as a bolus or as a continuous infusion over 1-5 days. Standard single agent doses range between 5-10 g/m^2. In the present study ifosfamide was given as a continuous 24-hour infusion for the patient's convenience. The combination of these two drugs could be of major interest in tumors where both of them are effective.

This phase I study on the combination of docetaxel and ifosfamide was performed with the following objectives: 1) to determine the maximum

tolerated dose (MTD), 2) to characterize the toxic effects, 3) to determine the optimal drug administration sequence, 4) to propose a dose and sequence for further phase II studies, 5) to report any antitumor effect of the docetaxel-ifosfamide combination, 6) to describe pharmacokinetics of both drugs in this particular combination. The results of the latter topic will be published elsewhere. Rowinsky *et al.* demonstrated the importance and potential relevance of drug sequence (34) and therefore sequence investigations should be integrated in all phase I studies involving combinations of drugs.

PATIENTS AND METHODS

Eligibility

Only patients with a histologically confirmed solid tumor for which no therapies with greater potential benefit than docetaxel and ifosfamide existed were candidates for this study. Eligibility criteria further included: 1) age $\geq$ 18 years and $\leq$ 75 years; 2) WHO performance status 0-2; 3) no more than one line of previous chemotherapy for advanced disease; prior (neo) adjuvant chemotherapy was allowed provided that this chemotherapy had ended at least 6 months before study entry; 4) off previous anticancer therapy for more than 4 weeks (6 weeks in case of nitrosureas, mitomycin C and carboplatin); 5) no prior treatment with docetaxel, ifosfamide or paclitaxel; 6) off previous radiotherapy for at least 4 weeks (8 weeks in case of extensive prior radiotherapy); 7) adequate bone marrow- (neutrophils $\geq$ 2 x 10^9/l, platelets $\geq$ 100 x 10^9/l), hepatic- (total bilirubin $\leq$ 1.25 times the upper-normal limits, ASAT (SGOT) $\leq$ 2 times and in case of proven liver metastases $\leq$ 3 times the upper-normal limits) and renal function (serum creatinine $\leq$ 120 μmol/l); 8) absence of symptomatic peripheral neuropathy $\geq$ grade 2 according to NCI Common Toxicity Criteria (CTC) (35); 9) no peptic ulcer, unstable diabetes mellitus or other contra-indications for the use of corticosteroids. All patients had to give written informed consent.

Drug administration

Docetaxel (Taxotere®-RP 56976) was supplied by Rhône-Poulenc Rorer (Antony, France) as a concentrated sterile solution containing 40 mg/ml = 80 mg/2 ml/vial in polysorbate 80 (Tween®80). The appropriate amount of the drug to be administered to the patient was diluted in 5% dextrose- or 0.9% saline solution so that the maximum docetaxel concentration was 1 mg/ml. The drug was administered to the patient as a 1-hour IV infusion.

Ifosfamide (ASTA, Degussa, Frankfurt, Germany) was diluted in a 3 l dextrose saline solution plus mesna and administered to the patient as a 24-hour IV continuous infusion. Treatment cycles were repeated every 3 weeks.

Routine comedication

All patients received 32 mg of methylprednisolone or 8 mg of Dexamethasone orally 12- and 3 hours before docetaxel infusion and than 12- and 24 hours after the end of docetaxel infusion, followed by either 32 mg or 8 mg twice daily for an additional 3 days in order to prevent the onset of hypersensitivity reactions and to reduce and/or delay the occurrence of skin toxicity and/or fluid retention related to docetaxel.

Prophylactic comedication with mesna was given to all patients in order to prevent urotoxicity induced by ifosfamide. The mesna dose was adapted according to the ifosfamide dose and was fractionated in an IV bolus of 20% of the corresponding ifosfamide dose given just before ifosfamide administration, 50% of the dose given concomitantly with the ifosfamide solution and 20% of the dose in a 2 l dextrose saline solution given as a 12-hour infusion after the end of ifosfamide administration.

All patients received prophylactic i.v. anti-emetic medication with a 5-HT_3 antagonist in a dose of either 8 mg of ondansetron, 5 mg of Tropisetron or 3 mg of Granisetron, just before the first cytotoxic drug administration and then once a day orally during the 2 following days in the same dose.

Dosage

The docetaxel and ifosfamide doses were escalated according to a

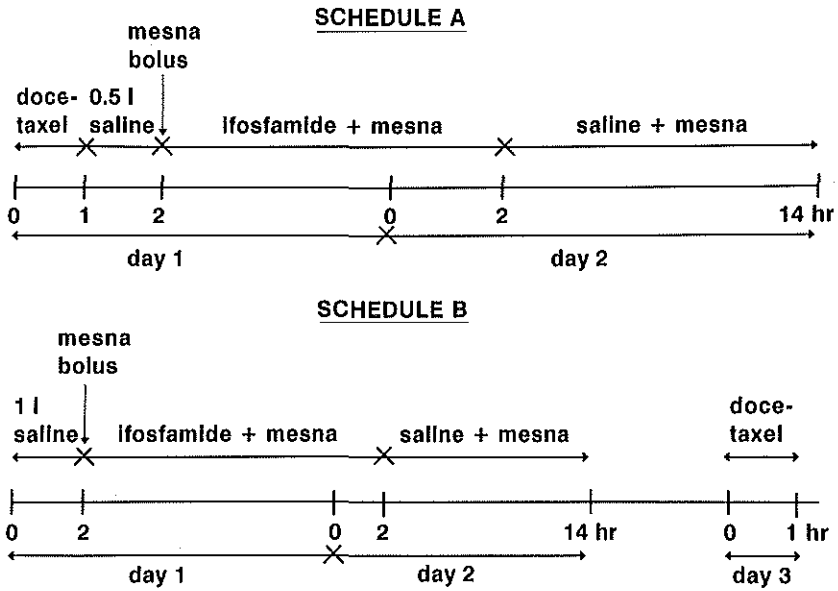
preestablished schedule and according to the toxicities observed at the previous dose-level, after a minimum of 3 patients had tolerated the previous dose. Toxicities were graded according to the NCI Common Toxicity Criteria (CTC) (35). Once a patient in a given dose-level developed side effects of CTC $\geq$ grade 3, other than myelosuppression, an additional 3 patients were entered at the same dose level. Dose limiting toxicity (DLT) was defined as CTC $\geq$ grade 3 toxicity (excluding myelotoxicity) observed in $\geq$ 3 patients at a given dose-level. For myelosuppression DLT was defined as: 1) granulocytes $< 0.5 \times 10^9$/l for $>$ 7 days; 2) granulocytes $< 1.0 \times 10^9$/l with fever $\geq$ 38°C lasting $>$ 3 days; 3) platelets $< 25 \times 10^9$/l; 4) infections $\geq$ grade 3 requiring hospitalization.

The maximum tolerated dose (MTD) was defined as the dose level at which at least 3 out of 6 patients developed a same dose limiting toxicity. In this study MTD's could be determined for the 2 drug sequences.
The following dose levels of docetaxel/ifosfamide were explored: level I 60 mg/m^2/2.5 g/m^2, level II 75 mg/m^2/2.5 g/m^2, level III 75 mg/m^2/3.0 g/m^2, level IV 75 mg/m^2/4.0 g/m^2, level V 75 mg/m^2/5.0 g/m^2, level VI 85 mg/m^2/5.0 g/m^2, level VII 100 mg/m^2/5 g/m^2.

Drug sequence

Dose escalation was initially performed with docetaxel preceding ifosfamide (schedule A) with a 1 hour interval between the end of docetaxel infusion and the start of ifosfamide (fig. 1). When the MTD and doses to be used for further phase II studies were determined for schedule A, the dose-level just below the MTD was reassessed with ifosfamide preceding docetaxel (schedule B). In this schedule there is a 24 hour interval between the end of ifosfamide infusion and the start of docetaxel infusion. When the toxicities in this schedule were acceptable, further dose escalation was pursued.

FIGURE I: DRUG ADMINISTRATION SEQUENCE



Pretreatment and follow-up studies

Prior to the start of treatment medical history was taken and physical examination including neurological examination, laboratory studies, ECG, chest X-ray and if appropriate CT scan were performed.

Laboratory studies included a complete blood, count, differential white blood cell (WBC) count, sodium, potassium, chloride, bicarbonate, creatinine, urea, magnesium, calcium, total protein, albumin, alkaline phosphatase, bilirubin, *y*-GT, LDH, ASAT (SGOT), ALAT (SGPT), glucose, uric acid and urinalysis.

History, physical examination, toxicity scoring (according to NCI CTC) (35) were performed every 3 weeks and laboratory studies weekly. Complete blood counts were performed every week and every 2 days in case of febrile neutropenia. Urinalysis was performed before, during and after ifosfamide administration in every cycle. Every 3 weeks ECG was repeated. Chest X-rays

and formal tumor assessments were performed after every 2 courses of chemotherapy. Standard WHO response criteria (36) were used.

RESULTS

Thirty-four patients were entered in this study. Patients characteristics are given in Table I. All patients were evaluable for toxicity and tumor response. Table II represents the dose level studied, the number of patients at each dose level and the number of evaluable courses at each dose level. Fifteen patients were treated at more than one dose level because of dose reduction due to various toxicities. Ten of these 15 patients underwent dose reduction after the first treatment cycle because of neutropenic fever. The other 5 patients underwent dose reduction after 2 or more courses. Two patients at dose level VIA underwent 3 and 4 dose reductions respectively. The number between brackets represents the number of patients who were initially treated at a higher dose level and underwent dose reduction. A total of 155 courses were assessable for toxicity. No dose limiting toxicities were observed for cycle 1 in dose levels IA and IIA. Serious toxicities were reported in cycle 1 at the following dose levels: febrile neutropenia at dose levels IIIA-VIA and IVB, diarrhea grade 4 at dose level VA and vomiting grade 3 at dose level IVB. A septic death was reported at dose level VA.

Hematologic toxicity

Table III represents the relevant hematological toxicities. Granulocytopenia grade 3 and 4 were observed at all dose levels in 89% of courses and appeared to be ifosfamide dose-dependent. In schedule A febrile neutropenia associated with hospital admission occurred in 15% of courses of which only 1 course was associated with sepsis. The granulocyte nadir was normally observed between day 8 and 11 of the course and lasted shorter than 7 days. Severe anemia grade 3 and 4 were only documented in 6% of the courses. Thrombocytopenia grade 1 and 2 were observed at all dose levels but grade 3 and 4 were not reported.

TABLE I: PATIENT CHARACTERISTICS

Characteristics		Number
Patients treated:		34
Age years	median	53
	range	(26-69)
WHO performance status:	median	1
	range	(0-1)
Sex:	male/female	24/10
Prior chemotherapy treatment:	none	11
	1 regimen	23
Tumor type:		
head and neck cancer		5
non-small cell lung cancer		5
malignant melanoma		5
soft tissue sarcoma		3
malignant mesothelioma		3
primary unknown		2
colon cancer		2
miscellaneous		9

TABLE II: PATIENT ACCRUAL

Dose level	docetaxel (mg/m^2)	ifosfamide (g/m^2)	Number of pat. (*)		Number of cycles (range)	
I A	60	2.5	3	(1)	7	(1-2)
II A	75	2.5	3	(3)	29	(1-10)
III A	75	3.0	6	(4)	24	(1-9)
IV A	75	4.0	6	(5)	32	(1-8)
V A	75	5.0	7	(3)	33	(1-14)
VI A	85	5.0	3		5	(1-3)
III B	75	3.0	-	(3)	8	(1-4)
IV B	75	4.0	6		17	(1-6)
Total			34		155	

(*) Patients initially treated at a higher dose level.

In schedule B granulocytopenia grade 3 and 4 were documented in 77% of the courses. Febrile neutropenia occurred in 18% of the courses while only 2 courses were complicated by sepsis. Severe anemia and thrombocytopenia grade 3 and 4 were uncommon.

Non-hematologic toxicity

The most common non-hematologic toxicities are shown in table IV. Alopecia was common and occurred at all dose levels. Nausea and vomiting were usually mild and were reported in 41% and 25% of courses respectively. In schedule B grade 3 vomiting was observed in 3 courses. Diarrhea grade 1 and 2 occurred in 8% of courses being severe (grade 4) in only 1 course at dose level VA. Mucositis grade 1 and 2 were documented in 24% of courses, being severe in 1 course at dose level VIA and in 1 course at dose level IIIB. The incidence of gastrointestinal toxicity appeared to be higher in schedule B. Asthenia occurred at all dose levels and was not related to schedule. The docetaxel-ifosfamide combination induced a mild sensory neuropathy grade 1-2 in 56% of patients. However, no neurocortical toxicities such as ifosfamide-induced encephalopathy were observed. Docetaxel related toxicities such as skin- and nail changes and edema were mild and never a reason to stop therapy. They occurred in 38%, 24% and 15% of patients respectively. Hypersensitivity reactions were mild to moderate and consisted of flushing and dyspnea in some patients. They only occurred in 5% of courses but were more frequent in schedule B.

Responses

A histologically proven complete response (CR) was achieved in a patient with a soft tissue sarcoma treated at dose level II. Partial responses were observed in cancer of unknown primary and in non-small cell lung cancer, 1 patient each.

TABLE III: HEMATOLOGIC TOXICITY

	Dose level								
	I A	II A	III A	IV A	V A	VI A	III B	IV B	Total (%)
Number of assessable patients (*)	3 (1)	3 (3)	6 (4)	6 (5)	7 (3)	3	- (3)	6	34
Courses assessable for hematologic toxicity	7	29	24	32	33	5	8	17	155
Number courses with:									
- gr. 3 neutropenia	-	8	4	1	-	-	1	3	17 (11)
- gr. 4 neutropenia	3	18	17	30	33	5	5	10	121 (78)
- febrile neutropenia	-	3	3	8	7	2	-	3	26 (17)
- gr. 1-2 thrombocytopenia	2	1	1	1	8	1	-	1	15 (10)
- gr. 3-4 thrombocytopenia	-	-	-	-	-	-	-	-	0 (0)

* Patients initially treated at a higher dose level.

DISCUSSION

Docetaxel is a new antimicrotubule agent that has already demonstrated activity in a wide variety of solid tumors and was registered for use in advanced breast cancer in 1995.

Ifosfamide is an alkylating agent that is active a.o in non-small cell lung cancer, testicular cancer, breast cancer and sarcoma. Because of the only partly overlapping toxicity profiles and their activity against a wide range of solid tumors it was considered of interest to pursue a combination regimen of these two drugs. This phase I study was performed to assess the feasibility of the combination, to determine the MTD and the side effects and to evaluate if toxicity is drug sequence-dependent.

No phase I studies on the combination docetaxel-ifosfamide have been performed earlier. The major toxicity of the combination was granulocytopenia grade 3 and 4 which occurred in 89% of all courses and appeared to be ifosfamide dose dependent. Neutropenia grade 4 associated with fever occurred in 17% of all courses and was more common at the highest dose levels. The DLT for schedule A was neutropenic fever at a dose of 85 mg/m^2 of docetaxel and 5 g/m^2 of ifosfamide (dose level VIA). The DLT for schedule B was neutropenic fever at a dose level of 75 mg/m^2 of docetaxel and 4 g/m^2 of ifosfamide (dose level IVB), which was the initial dose tested. This observation can not be explained by a difference in hematologic toxicity between schedule A and B nor by a difference in patients selection. Sincé this made clear that there was no obvious advantage of this schedule as compared to schedule A, no further patients have been studied. The most common non-hematologic toxicities were nausea, vomiting, mucositis and diarrhea, most of them being mild. Schedule B appeared to induce more gastrointestinal toxicity than schedule A, for which no explanation can be given. In 19 of 34 evaluable patients (56%) the docetaxel-ifosfamide combination induced a sensory neuropathy grade 1-2, while no neurocortical toxicity was observed. The incidence of sensory neuropathy of the combination was slightly higher than the incidence reported for docetaxel as a single agent (49%) (37).

TABLE IVA: NON-HEMATOLOGIC TOXICITY

	Dose level								
	I A	II A	III A	IV A	V A	VI A	III B	IV B	Total (%)
Number of assessable patients(*)	3 (1)	3 (3)	6 (4)	6 (5)	7 (3)	3	- (3)	6	34
Number of assessable courses	7	29	24	32	33	5	8	17	155
Number of courses with:									
- nausea gr. 1/2	5	1	9	13	13	5	7	11	64 (41)
- nausea ≥ gr. 3	-	-	-	-	-	-	-	-	0 (0)
- vomiting gr. 1/2	-	-	2	7	11	5	4	9	38 (25)
- vomiting ≥ gr. 3	-	-	-	-	-	-	2	1	3 (2)
- mucositis gr. 1/2	-	3	2	7	11	2	3	9	37 (24)
- mucositis ≥ gr. 3	-	-	-	-	-	1	1	-	2 (1.3)
- diarrhea gr. 1/2	-	1	3	2	1	2	-	3	12 (8)
- diarrhea ≥ gr. 3	-	-	-	-	1	-	-	-	1 (0.6)
- myalgia	-	4	3	7	-	1	1	3	19 (12)
- allergy	-	-	1	-	-	-	1	5	7 (5)

* Patients initially treated at a higher dose level

TABLE IVB

	I A	II A	III A	IV A	V A	VI A	III B	IV B	Total (%)
Number of assessable patients (*)	3 (1)	3 (3)	6 (4)	6 (5)	7 (3)	3	- (3)	6	34
Number of patients with:									
- alopecia gr. 1/2	3	3 (1)	5 (1)	5 (1)	6	3	-	6	34 (100)
- asthenia gr. 1/2(**)	2	3 (1)	2 (2)	4 (1)	4	1	-	6	26 (76)
- asthenia gr. 3(**)	-	-	-	1	-	-	-	-	1 (3)
- cutaneous	-	1	2	3	3	1	2	1	13 (38)
- nails	-	1 (1)	- (1)	1	1 (1)	-	1	1	8 (24)
- edema gr. 1/2(**)	-	1 (1)	-	-	2	-	-	1	5 (15)
- neurosensory gr. 1/2	-	2	1 (1)	4	6 (1)	1	-	3	19 (56)
- neurocortical	-	-	-	-	-	-	-	-	0 (0)

* Patients initially treated as a higher dose level

** grade 1 = mild, grade 2 = moderate, grade 3 = severe.

In a phase I study combining paclitaxel and cisplatin (34) and in a phase I study on the docetaxel-cisplatin combination (38, 39) the incidence of sensory neuropathy of the combination was higher than that reported for docetaxel as a single agent (37). It was suggested that these agents act synergistically in producing neurotoxicity.

The incidence of docetaxel related toxicities like hypersensitivity reactions, nail- and skin toxicity and edema was relatively low and never a reason for treatment discontinuation. In this study all patients received premedication consisting of dexamethasone or methylprednisolone, which might account for the low incidence of the above mentioned side effects.

Antitumor responses were seen in a variety of tumor types at all dose levels. Of note was the histologically proven complete response in a patient with soft tissue sarcoma.

Based upon the data obtained in this phase I study the recommended dose for phase II studies will be 75 mg/m^2 of docetaxel combined with 5 g/m^2 of ifosfamide. Schedule A is advocated for further treatment because this schedule is more manageable and seems to induce less gastrointestinal toxicity than schedule B.

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THE VENOTONIC DRUG HYDROXYETHYLRUTOSIDEN IS UNABLE TO PREVENT OR REDUCE DOCETAXEL INDUCED FLUID RETENTION. RESULTS OF A COMPARATIVE STUDY

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SUMMARY

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 database available at the manufacturer (Rhône-Poulenc Rorer) was that patients who received venotonic drugs appeared to tolerate more courses of docetaxel. This prompted a comparative study to investigate if the venotonic drug hydroxyethylrutosiden could reduce or delay docetaxel-related fluid retention. Eighty-five patients with metastatic breast cancer who were treated with docetaxel at a dose of 100 mg/m^2 with corticoid co-medication were allocated to receive either hydroxyethylrutosiden 300 mg given orally 4 times daily (group A) or no hydroxyethylrutosiden (group B). Endpoint for analysis was development of fluid retention $\geq$ grade 2. Fluid retention $\geq$ grade 2 was reported in 14 of 42 patients (33%) of group A and in 15 of 43 patients (35%) of group B and occurred after a median number of 4 cycles of docetaxel in both groups. Weight gain was similar in group A and B. We conclude that hydroxyethylrutosiden does not reduce or delay the incidence and severity of docetaxel-related fluid retention.

INTRODUCTION

Fluid retention which includes peripheral edema, ascites, pleural- or pericardial effusion or a combination of these is a cumbersome 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 $\geq$ 400 mg/m^2 (1, 2). Recent data suggest that with corticosteroid co-medication, initially intended to reduce hypersensitivity reactions, fluid retention is delayed and reduced (3). The addition of antihistamines or 5HT2 blockers to the co-medication schedule does not influence the occurrence in

severity or frequency.

A remarkable suggestion from the data base available at the manufacturer (Rhône-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 administered no definitive conclusions on the value of these drugs could be given.

Hydroxyethylrutosiden (Venoruton) is a standardised mixture of semisynthetic flavonoids, which acts primarily 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 also has a possible protective effect on the vascular endothelium (4). Hydroxyethylrutosiden (Venoruton) is a registered and widely used drug in the Netherlands. At the recommended dose of 300 mg given orally 4 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 c.q. reduction of docetaxel related fluid retention.

PATIENTS AND METHODS

Eligibility

Patients with histologically or cytologically proven breast cancer who started treatment with docetaxel and had given oral informed consent were entered in this study.

Eligibility criteria further included: 1) age $\geq$ 18 years; 2) WHO performance status 0-2; 3) adequate hematological- (granulocytes $\geq$ 2.0 x 10^9/l), renal- (serum creatinine $\leq$ 1.5 x upper normal limit) and hepatic function (total serum bilirubin $\leq$ 1.25 x upper normal limit); 4) no pre-existing pleural fluid, ascites or peripheral edema, unless pleuritis carcinomatosa and/or peritonitis carcinomatosa.

Drug administration

Docetaxel was supplied by Rhône-Poulenc Rorer (Antony, France) as a concentrated sterile solution containing 40 mg/ml in a 2 ml vial in polysorbate 80 (Tween®80). The appropriate amount of the drug to be administered to the patient was diluted in 5% dextrose solution (or 0.9% saline serum) so that the maximum docetaxel concentration was 1 mg/ml. The drug was administered to the patient as a one hour infusion every 3 weeks. All patients received co-medication consisting of dexamethasone 8 mg orally 13-, 7- and 1 hour(s) before docetaxel infusion, followed by dexamethasone 8 mg orally twice a day during 96 hours after docetaxel administration. In addition patients were allocated to: a) 4 oral administrations of 300 mg hydroxyethylrutosiden daily until docetaxel discontinuation or the development of fluid retention $\geq$ grade 2; b) no hydroxyethylrutosiden.

Study parameters

Prior to the start of treatment history was taken and 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 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. During docetaxel treatment weight was measured and physical examination was performed every 3 weeks in order to reveal potential signs of fluid retention. A CT-scan of the thorax or an X-ray of the chest, if not already indicated to follow tumor parameters, were performed every 2 treatment cycles. Because there is no WHO or CTC grading for edema or effusion, this was graded as follows:

Peripheral edema:

grade 0: no edema
grade 1: no visual changes, pitting effects
grade 2: visual and pitting edema
grade 3: massive edema, loss of externally visual joint anatomy
grade 4: incapacitating edema

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, legs, pleural effusion, pericardial effusion, ascites and generalized edema.

Statistical analysis

Patients were allocated to treatment with hydroxyethylrutosiden or no treatment. The primary endpoint for analysis was development of fluid retention $\geq$ grade 2. Patients with pre-existing 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. Time to treatment failure was defined as the first cycle after which fluid retention $\geq$ 2 was observed. Some patients received diuretics because of occurring mild fluid retention, not yet of grade 2. These patients were not considered as failures in the analysis, but censored at the start of diuretics. Patients who did not develop a grade 2 fluid retention and were not treated with diuretics, but stopped treatment for other reasons, were censored after the last treatment cycle. The logrank test was used to test for a difference in the probability of development of fluid retention $\geq$ grade 2

between the 2 treatment groups.

RESULTS

A total of 85 patients were entered into this study of whom 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 I. At the start of treatment 19 patients had a pleuritis carcinomatosa. Two patients with edema of the arms and 1 patient with edema of the leg (all grade 1) were included in the analyses and evaluated for the development of a higher grade of edema and/or edema at another site.

The number of evaluable treatment cycles varied between 1 and 11, median 4 cycles, and was similar in both groups. Forty patients did not develop fluid retention or an increase in fluid retention (in case of pre-existing edema), while 16 patients developed a maximum grade 1, 21 patients a grade 2 and 8 patients a grade 3 fluid retention (table II). The incidence of fluid retention $\geq$ grade 2 was similar for group A and 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 before fluid retention $\geq$ grade 2 developed ($n = 29$) was 4 cycles (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 were still at risk for development of fluid retention.

Figure 1 shows the actuarial probability of development of fluid retention $\geq$ grade 2 in both groups. The actuarial probability after 6 cycles is approximately 45% and similar in both groups (logrank test: $p > 0.20$).

Only 45 patients experienced a consistent increase in weight after at least 1 cycle compared to pretreatment with a median maximum increase in weight of 5.5% (range 0.3-32%). This maximum increase was observed after a median of 4 cycles. On the other hand most of the patients showed a (sometimes minor) decrease in weight after at least 1 cycle compared to pretreatment with a median decrease of 3.3%.

TABLE I: PATIENT CHARACTERISTICS

		Treatment	
		Hydroxyethylrutosiden	Control
Number of patients		42	43
age (years)	median range	48 31-68	50 31-73
Type and grade 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

The most important reason to stop the study was discontinuation of treatment with docetaxel due to progressive disease and/or toxicity in 25 patients (60%) of group A and in 22 patients (51%) of group B. In 7 patients (17%) of group A and in 15 patients (35%) of group B diuretics were given because of development of fluid retention. In 1 patient of group A and in 4 patients of group B diuretics were administered although there was no fluid retention $\geq$ grade 2. In 6 patients of group A and group B the study was discontinued because of toxicity alone that consisted of edema in 5 patients of each group.

DISCUSSION

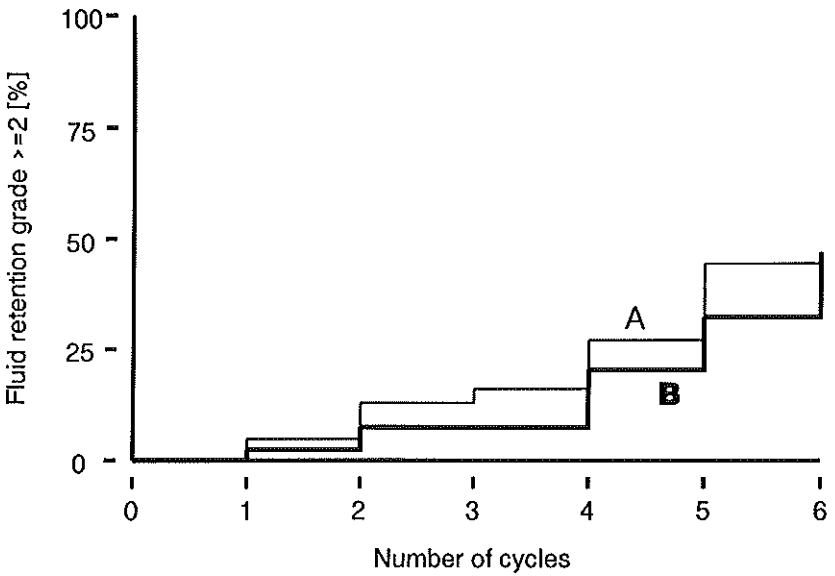
Fluid retention is one of the most troublesome side effects of docetaxel. It appears to be related to the cumulative dose, increasing in incidence at cumulative doses of $\geq$ 400 mg/m^2 (1, 2).

TABLE II: GRADE, TYPE AND CYCLE OF MAXIMUM FLUID RETENTION

	Treatment	
	Hydroxyethylrutosiden	Control
Grade max fluid retention		
1	6	10
2	9	12
3	5	3
Type max fluid retention		
arm	6	8
leg	9	14
pleura	5	0
general	0	3
Cycle fluid retention ≥ grade 2		
median	4	4
range	1-9	1-9

The incidence of fluid retention reported in various phase II studies ranges from 9-89% (3, 5-12). The EORTC Clinical Screening Group investigated whether prophylactic premedication that consisted of dexchlorpheniramide 5 mg IV and ranitidine 50 mg IV 30 minutes before docetaxel administration plus prednisolone 130 mg orally 12 and 6 hours before chemotherapy could reduce the incidence and severity of fluid retention observed in other studies (5). In 37 evaluable patients fluid retention occurred in 89.2% of patients 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 to onset of fluid retention was 301 mg/m^2 and to treatment discontinuation due to fluid retention 698 mg/m^2. The investigators concluded that the above mentioned premedication failed to reduce and/or delay the incidence of fluid retention.

FIGURE 1: THE ACTUARIAL PROBABILITY OF DEVELOPMENT OF FLUID RETENTION ≥ GRADE 2 IN GROUP A AND B



In a phase II study of the EORTC Breast Cancer Study Group docetaxel was administered at a dose of 50 mg/m^2 on day 1 and 8 every 3 weeks, and patients were randomized between prophylactic oral antihistamine with or without methylprednisolone (3). Of 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 of dexamethasone orally twice a day starting one day before docetaxel infusion and to be continued for 96 hours after docetaxel administration, is routinely applied.

A remarkable suggestion from the data base available at the manufacturer (Rhône-Poulenc Rorer) was that patients who received a so-called venotonic

drug were able to 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, which acts primarily on the microvascular endothelium to reduce hyperpermeability and edema. Furthermore it improves the microvascular perfusion and microcirculation, and reduces the erythrocyte- and platelet aggregation while the erythrocyte deformability is preserved (4). 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 (13-15). In these studies patients with post-mastectomy lymphedema of the arm and/or lymphedema of the leg of various causes were randomized between treatment with benzopyrones or with placebo. The conclusion of these studies was that treatment with benzopyrones resulted in a slow reduction of lymphedema of the extremities and an improvement in general well-being.

Until now no comparative studies have been performed to asses 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 treated with docetaxel and all receiving corticosteroid co-medication, were entered. Patients were allocated to 4 oral administrations of 300 mg hydroxyethylrutosiden daily or to no hydroxyethylrutosiden. The primary endpoint for analysis was development of fluid retention $\geq$ grade 2. Forty-two patients were allocated to treatment with hydroxyethylrutosiden (group A) while 43 patients were allocated to the control arm (group B). Forty patients did not develop fluid retention or an increase in fluid retention. In 14 patients (33%) of group A and in 15 patients (35%) of group B fluid retention $\geq$ grade 2 occurred that was located in the extremities in most patients. In both groups fluid retention $\geq$ grade 2 was documented after a median number of 4 cycles of docetaxel treatment.

Forty-five of all patients showed weight gain that ranged from 0.3-31.8% with a median of 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 1 patient of group A and in 4 patients of group B diuretics were started although no fluid retention ≥ grade 2 was scored. As the decision to start diuretics in case of mild fluid retention could have been influenced by the knowledge of whether or not the patient received hydroxyethylrutosiden in this open, not placebo controlled comparative study, we have censored these 5 patients in our analysis with time to objective grade 2 fluid retention as primary endpoint.

We conclude that hydroxyethylrutosiden does not reduce or delay the incidence and severity of docetaxel-related fluid retention. In view of the fact that 45% of all patients developed fluid retention ≥ grade 2 after 6 cycles despite corticosteroid co-medication, there is a need for further studies on the prevention of this troublesome side-effect.

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CORTICOSTEROID COMEDICATION DOES NOT REDUCE INCIDENCE AND SEVERITY OF NEUROTOXICITY INDUCED BY DOCETAXEL

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(submitted)

SUMMARY

Background

Docetaxel is a new antimicrotubule agent that induces a predominantly sensory neuropathy that is mild in most patients. This prospective study was performed to determine if corticosteroid comedication reduces the incidence and severity of docetaxel-induced neuropathy.

Patients and methods

Two groups of patients treated with docetaxel in subsequent cohorts were prospectively analyzed for neurotoxicity. Group A consisted of 38 patients with a variety of solid tumors, who were treated in studies before corticosteroid comedication was recommended, while 49 female patients in group B with metastatic breast cancer were treated after comedication with corticosteroids was introduced as a routine. Neuropathy was evaluated by a clinical sum-score for symptoms and signs and by measurement of the Vibration Perception Threshold (VPT). The severity of neuropathy was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Results

In 42% of patients of group A and in 65% of patients of group B a mainly mild neuropathy was documented. There was no statistically significant difference in neurotoxicity between group A and B. The cumulative dose of docetaxel showed a significant correlation with post-treatment scores of VPT, sensory sum-score, grade of paresthesias, and grade of neurosensory- and neuromotor toxicity.

Conclusion

Corticosteroid comedication does not reduce the development of docetaxel-related neuropathy.

INTRODUCTION

Docetaxel (Taxotere, Rhône-Poulenc Rorer, Antony, France) is a new semi-synthetic taxoid that is prepared from 10-deacetyl baccatin III, a non-cytotoxic precursor extracted from the needles of the European Yew, Taxus Baccata. Like paclitaxel (Taxol), docetaxel acts as an antimicrotubule agent that enhances polymerization of the tubulin into stable microtubules and inhibits microtubule depolymerization. This leads to a disruption of the equilibrium within the microtubule system and ultimately to cell death (1-4).

In phase I studies on single agent docetaxel the major dose limiting toxicity (DLT) was neutropenia that appeared to be short-lasting, dose-dependent, schedule-independent and non-cumulative (5-10). Based on these phase I studies the recommended single agent dose and schedule for docetaxel was 100 mg/m^2 given as a one hour infusion every 3 weeks. Phase II studies on docetaxel showed activity in breast cancer (11-15), non-small cell lung cancer (16-18), head- and neck cancer (19), gastric cancer (20), melanoma (21), soft tissue sarcoma (22), and pancreatic cancer (23). The most important side effect was an early short-lasting neutropenia which in 20% of the patients was complicated by infection (1). Other side effects included alopecia, nausea, vomiting, diarrhea, mucositis, asthenia, infrequent hypersensitivity reactions, skin reactions, nail changes, fluid retention and a mild sensory neuropathy (1, 24-26).

We prospectively assessed neurotoxicity in 41 patients treated with docetaxel as first- or second line chemotherapy. Docetaxel induced a predominantly sensory neuropathy in 20 of 41 patients that was mild in most patients. However, at cumulative doses above 600 mg/m^2, 3 of 15 patients developed a moderate and 1 of 15 patients a severe neuropathy (24). Most of these patients did not receive corticosteroid comedication. In the present study we prospectively assessed neurotoxicity in patients with metastatic breast cancer who were treated in a multicentre study of docetaxel, and who routinely received corticosteroid comedication during five days. The results of this prospective study were compared with those of the previous study (24), with

the aim to determine if corticosteroid comedication reduces and/or delays docetaxel-induced neurotoxicity.

PATIENTS AND METHODS

Eligibility

In two groups of patients with metastatic or locally advanced cancer neurotoxicity was assessed prospectively. Group A included patients with metastatic or locally advanced cancer who participated to one of four different multicentre phase II trials on the activity of docetaxel as first- or second line chemotherapy as described before (24). The patients with breast cancer who were randomized to receive prophylactic corticosteroids were excluded from the analyses. Group B consisted of patients with histologically or cytologically proven breast cancer who had not responded to conventional chemotherapy and participated to a compassionate use programme. Eligibility criteria for all studies included: 1) age $\geq$ 18 years; 2) WHO performance status 0-2; 3) adequate hematological- (granulocytes $\geq$ 2.0 x 10^9/l), renal- (serum creatinine $\leq$ 1.5 x upper normal limit) and hepatic function (total serum bilirubin $\leq$ 1.25 x upper normal limit); 4) no clinical signs of symptomatic peripheral neuropathy grade 2 or more according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) (27). All patients had given informed consent.

Drug administration

Docetaxel was supplied by Rhône-Poulenc Rorer (Antony, France) and administered as a one hour infusion at a dose of 100 mg/m^2 every 3 weeks. In six patients of group A the dose per cycle was divided and given on days 1 and 8 every 3 weeks (28). In group B all patients received comedication consisting of 8 mg of dexamethasone orally 13,7, and 1 hour(s) before docetaxel infusion, followed by dexamethasone 8 mg orally twice a day during 96 hours after docetaxel administration. In group A no corticosteroids were given because these patients were treated in studies before corticosteroid comedication was recommended. No other neurotoxic drugs were used during the study or follow-

up period.

Methods

The severity of neuropathy was evaluated by a questionnaire for neurologic symptoms, by standardized neurological examination and by measurements of the Vibration Perception Threshold (VPT) before start of treatment, after every two cycles, at 2 weeks after the last dose of docetaxel, and every 3 months thereafter. The questionnaire established separately absence (0) or presence (1) of paresthesias, numbness, loss of dexterity and unsteadiness of gait. On sensory examination, position sense, vibration sense, pin-prick sensation, Romberg's sign, Romberg's sign with heel-to-toe stand and tendon-reflexes of the legs were each scored as normal (0) or abnormal (1). A sum-score for these signs and symptoms was calculated (minimum 0, maximum 11). The severity of paresthesias was graded on a 5-point scale (0, no; 1, temporary; 2 continuous light; 3, severe; 4, unbearable). Sensory loss was defined as an abnormal test on either position sense, vibration sense or pin-prick sense. Patients were asked whether they experienced Lhermitte's sign or pain. Distal muscle strength in the lower extremities was tested. Motor signs were defined as the presence of objective weakness. The severity of neuropathy was scored according to the NCI Common Toxicity Criteria (CTC) (27) for sensory neuropathy (0, no symptoms or signs; 1, mild paresthesias, loss of deep tendon reflexes; 2, moderate paresthesias, objective sensory loss; 3, severe paresthesias, sensory loss interfering with function). VPT was measured at the dorsum of the second metacarpal bone of the left hand with a Vibrameter type IV (Somedic AB, Stockholm, Sweden) and recorded in micrometers of skin displacement. This Vibrameter uses a vibratory frequency of 100 Hz and corrects for pressure-induced alterations of vibratory amplitude. The mean value of three measurements of the VPT determined with the method of limits was considered the actual VPT (29). The VPT has been shown to be a reliable technique to monitor cisplatin neuropathy and shows a good correlation with the sum-score of neuropathic signs and symptoms as observed previously (30-32). It has been used to quantify paclitaxel-induced neuropathy

(33).

Since a relation was suggested between docetaxel-induced toxicity and cumulative dose given, as primary endpoint for the assessment of neurotoxicity the post-treatment evaluation on day 90 was chosen. Cycles of docetaxel given after the last neurologic evaluation, which occurred in 27 patients, were not counted in the analysis and excluded from the calculation of the cumulative dose.

Statistical methods

Primary endpoints for the analysis were the VPT, the sensory sum-score, the grade of paresthesias, the CTC neurosensory grade and the CTC neuromotor grade. Because of the skewed distribution of VPT the natural logarithm was used for statistical analysis. The post-treatment grade of patients with pre-existing paresthesias, CTC neurosensory or CTC neuromotor with grade $\geq$ 1 was considered 0 if it was not increased at post-treatment evaluation. Analysis of covariance was applied to test for a difference between the two treatment groups in post-treatment sensory sum-score and log VPT while adjusting for pre-treatment values, age and the cumulative dose of docetaxel (log transformed). Ordinal logistic regression analysis, according to the proportional odds model (34), was applied to compare the two groups with respect to post-treatment grade of paresthesias, neurosensory and neuromotor, adjusted for age and cumulative dose of docetaxel. The p-values reported in the results section for the comparison of groups A and B are all based on these adjusted analyses.

RESULTS

A total of 87 patients were evaluable for neurotoxicity. Patient characteristics are given in table I. The 2 groups we studied differed in several ways; group A consisted of patients with various tumor types of whom 9 patients had received cisplatin as prior antitumor therapy, whereas all patients of group B were females with metastatic breast cancer of whom most were

pretreated with non-neurotoxic chemotherapy. The patients with breast cancer in group A did not receive corticosteroid comedication. In both groups there was 1 patient with diabetes mellitus and 2 patients of group A reported alcohol abuse.

TABLE I: PATIENT CHARACTERISTICS

	Group A	Group B
Number of patients	38	49
Median age (y) (range)	52 (28-73)	50 (31-73)
Sex male	15	-
female	23	49
WHO Performance Status		
0	16	13
1	19	33
2	3	3
Prior treatment		
cisplatin	9	1
Oncovin	-	-
Other chemotherapy	15	45
Tumor type		
Breast	6	49
Ovarian	10	-
Sarcoma	7	-
Bladder	7	-
Head and neck	5	-
Melanoma	2	-
Colorectal	1	-

Table II represents the number of cycles and the cumulative dose of docetaxel administered for both groups. All patients started treatment at a dose of 100 mg/m^2 every 3 weeks, but in some patients dose reductions were required because of various adverse effects. In the 6 breast cancer patients of group A the dose per cycle was divided and given on day 1 and 8 every 3 weeks. The cumulative dose of docetaxel was $<$ 300 mg/m^2 in 15 patients of group A and in 10 patients of group B, 300-600 mg/m^2 in 9 patients of group A and in 15 patients of group B and $>$ 600 mg/m^2 in 14 and 24 patients of group A and B respectively.

TABLE II: NUMBER OF CYCLES AND CUMULATIVE DOSE OF DOCETAXEL

Number of cycles	Group A	Group B
median range	4 2-11	6 1-20
Cum. dose docetaxel mg/m^2		
median range	363 100-1100	575 100-1700

Before the start of treatment 4 patients in group A and 3 patients in group B showed a mild sensory neuropathy. The 4 patients in group A were pretreated with cisplatin. In table III the increase in sensory sum-score, VPT, paresthesias and grade of neurosensory and neuromotor toxicity are shown at post-treatment evaluation in relation to treatment group. According to CTC criteria 16 patients of group A (42%) and 32 patients of group B (65%) developed a sensory neuropathy. There was no statistically significant difference between groups A and B in the post-treatment scores of VPT ($p = 0.87$), sensory sum-score ($p = 0.83$), paresthesias ($p = 0.62$), and CTC neuromotor ($p = 0.53$). In group B somewhat higher CTC neurosensory grades were found compared to group A ($p = 0.04$).

Table IV represents the mean increase in sensory sum-score, the mean VPT ratio, the increase in severity of paresthesias, the CTC-neurosensory grade and the CTC-neuromotor grade at post-treatment evaluation classified by cumulative dose.

At a cumulative dose of docetaxel < 600 mg/m^2 6 of 24 patients in group A showed a mild sensory neuropathy, while in group B 8 of 25 patients developed a mild and 5 of 25 patients a moderate sensory neuropathy.
At a cumulative dose ≥ 600 mg/m^2 10 of 14 patients in group A developed a sensory neuropathy that was mild in 8 patients and moderate in 2 patients.

TABLE III: INCREASE IN NEUROTOXICITY IN RELATION TO TREATMENT GROUP

	Group A		Group B	
No. of assessable patients	38		49	
Sensory sum-score increase mean ± SD	2.5 ± 2.7		2.7 ± 2.2	
VPT ratio post/pre treatment mean ± SD	1.2 ± 0.7		1.5 ± 0.9	
	N	%	N	%
Paresthesias				
No increase	18	47	28	57
Grade 1	9	24	6	12
2	9	24	6	12
3	1	3	7	14
4	1	3	2	4
CTC Neurosensory				
No increase	22	58	17	35
Grade 1	14	37	21	43
2	2	5	9	18
3	0	0	2	4
CTC Neuromotor				
No increase	34	89	42	86
Grade 1	3	8	4	8
2	0	0	3	6
3	1	3	0	0

In group B 19 of 24 patients who had received a cumulative dose ≥ 600 mg/m^2 developed a sensory neuropathy that was mild in 13 patients, moderate in 4 patients and severe in 2 patients. Neuromotor toxicity was reported in 4 patients of group A and in 7 patients of group B. Neurotoxicity was a reason to stop docetaxel treatment in 3 patients (8%) of group A and in 6 patients (12%) of group B.

The cumulative dose of docetaxel showed a positive association with all post-treatment scores when adjusted for pretreatment score, age and treatment group: VPT ($p = 0.02$), sensory sum-score ($p < 0.001$), grade of paresthesias ($p = 0.11$), CTC neurosensory ($p < 0.001$), and CTC neuromotor ($p = 0.09$)

TABLE IV: INCREASE IN NEUROTOXICITY IN RELATION TO CUMULATIVE DOSE OF DOCETAXEL

	< 300 mg/m²		300-600 mg/m²		> 600 mg/m²	
Group	A	B	A	B	A	B
No. of patients	15	10	9	15	14	24
Sensory sum-score increase[1]	1.2 ± 1.1	0.6 ± 1.1	2.2 ± 2.2	3.3 ± 2.4	4.0 ± 3.4	3.1 ± 1.9
VPT ratio[2]	1.3 ± 0.9	1.1 ± 0.6	1.0 ± 0.2	1.3 ± 0.7	1.3 ± 0.8	1.8 ± 1.3
Paresthesias[3]						
no increase	9	8	4	6	5	14
Grade 1	5	1	2	3	2	2
2	1	0	3	3	5	3
3	0	1	0	1	1	5
4	0	0	0	2	1	0
CTC neurosensory[3]						
no increase	13	10	5	2	4	5
Grade 1	2	0	4	8	8	13
2	0	0	0	5	2	4
3	0	0	0	0	0	2
CTC neuromotor[3]						
no increase	15	9	9	13	10	20
Grade 1	0	1	0	1	3	2
2	0	0	0	1	0	2
3	0	0	0	0	1	0

(1) Difference between post-treatment and pre-treatment score. Values are means ± SD.

(2) Ratio of post-treatment and pre-treatment score. Values are means ± SD.

(3) Incidence at post-treatment evaluation; in case of pre-existing graded toxicities, only higher grades are counted.

DISCUSSION

Docetaxel (Taxotere, Rhône-Poulenc Rorer, Antony, France) is a new antimicrotubule agent that has shown activity in a variety of solid tumors (11-23). It induces a frequent dose-dependent, predominantly sensory neuropathy

that is mild in most patients (24-26). New *et al.* (25) reported a sensorimotor neuropathy in 11% of 186 patients that were treated with docetaxel at a wide range of cumulative doses (50-720 mg/m^2) and dose levels (10-115 mg/m^2). Hilkens *et al.* (4) documented a sensory neuropathy in 20 (49%) of 41 patients that was mild in most patients, but at cumulative doses of docetaxel higher than 600 mg/m^2 3 patients developed a moderate and 1 patient a severe neuropathy. The clinical characteristics of severe peripheral neuropathy were described in detail (35). Disabling and painful paresthesias, loss of tendon reflexes, loss of dexterity and steadiness of gait and proximal weakness dominated the clinical picture in these patients. In some patients Lhermitte's sign was observed (35,36). Freilich *et al.* (37) reported motor neuropathy due to treatment with docetaxel in 7 of 60 patients (12%). The motor weakness was predominantly proximal; it seemed idiosyncratic as it occurred at any stage of treatment and had a variable course. Motor neuropathy appeared to be reversible upon cessation of docetaxel therapy.

The present study was performed to determine if corticosteroid comedication reduces the incidence and/or severity of docetaxel-related neuropathy. In the early studies on docetaxel corticosteroid comedication was not given routinely. However, in a phase II study of the EORTC Breast Cancer Study Group in which patients treated with docetaxel were randomized between prophylactic oral antihistamine with or without methylprednisolone, corticosteroids appeared to decrease the severity of docetaxel-related fluid retention (28). Furthermore, the application of corticosteroid comedication markedly reduced the incidence of hypersensitivity reactions induced by docetaxel (38). Considering these observations it was recommended to administer corticosteroid comedication routinely in later studies on docetaxel.

Hilkens *et al.* performed a prospective study in which patients treated with docetaxel were assessed for neurotoxicity (24). Most of these patients did not receive corticosteroid comedication, except for some patients with breast cancer who participated in a phase II study in which patients were randomized to receive premedication with or without methylprednisolone (28). In the present analysis we deleted the patients who were randomized to receive

corticosteroid comedication (group A) and compared these data with the results of a study that prospectively assessed patients for neurotoxicity who were treated with docetaxel and received corticosteroid comedication (group B). The 2 groups differed in several ways; the patients in group A had a variety of tumor types and 9 of 38 patients were pretreated with cisplatin. The patients in group B however, were all females with metastatic breast cancer who were pretreated with non-neurotoxic chemotherapy.

There was no statistically significant difference in the post-treatment scores of VPT ($p = 0.87$), sensory sum-score ($p = 0.83$), paresthesias ($p = 0.62$), and CTC neuromotor ($p = 0.53$) when adjusted for pretreatment score, age, treatment group and cumulative dose of docetaxel. In group B somewhat higher CTC neurosensory grades were reported compared to group A ($p = 0.04$). This could be explained by the fact that the median number of cycles administered and the cumulative dose of docetaxel were higher in group B than in group A. The cumulative dose of docetaxel was strongly associated with all post-treatment neurotoxicity scores.

We conclude that corticosteroid comedication does not reduce the incidence or severity of docetaxel-related neuropathy. Nevertheless there is a role for corticosteroids since they do reduce the incidence of hypersensitivity reactions and docetaxel-related fluid retention.

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SUMMARY

In this thesis clinical and pharmacological studies on the antimicrotubule agent docetaxel in combination with cisplatin and ifosfamide respectively are described. The incidence of neurotoxicity induced by the combination of docetaxel with cisplatin and by single agent docetaxel were prospectively studied. In addition, studies were performed with the aim to reduce and/or delay docetaxel induced fluid retention and neurotoxicity, two frequent and sometimes disabling side effects.

In *chapter 1* an introduction is given about the development of a new class of antimicrotubule agents, the taxanes, that started with the extraction of paclitaxel from the bark of the Pacific Yew Taxus brevifolia in the late 1960s. This was followed by the development of docetaxel, a semisynthetic analog of paclitaxel, using a precursor extracted from the needles of the European Yew Taxus Baccata. Docetaxel has shown considerable activity in a variety of solid tumors.

Chapter 2 presents an overview of the preclinical and clinical studies on docetaxel as a single agent, the development of combinations of docetaxel with other drugs, and the side effects. In preclinical models docetaxel showed impressive cytotoxic activity. Phase I studies on docetaxel revealed that the major dose limiting toxicity was a short-lasting, dose-dependent, schedule-independent and non-cumulative neutropenia. Other toxic reactions were usually mild and included alopecia, nausea, vomiting, mucositis, diarrhea, neurotoxicity, infrequent hypersensitivity reactions, fluid retention and skin and nail toxicity. Responses were observed in a number of solid tumor types. For phase II studies the recommended dose and schedule was 100 mg/m^2 given as a 1-hour infusion every 3 weeks. Docetaxel appeared to have great therapeutic potential in advanced breast cancer.

Chapter 3 presents the results of a phase I and pharmacologic study of

docetaxel and cisplatin in patients with advanced solid tumors. This study was performed to assess the feasibility of the combination and to determine the maximum tolerated dose and the side effects with an emphasis on sequence-dependent side effects. A total of 64 patients were treated with docetaxel given as a 1-hour infusion followed by cisplatin as a 3-hour infusion (schedule A) or with cisplatin followed by docetaxel (schedule B). Docetaxel doses ranged from 55-100 mg/m^2 and cisplatin doses from 50-100 mg/m^2. Leukocytopenia and neutropenia were common (overall 90%; grade 3 or 4 87%) short-lasting and docetaxel dose-dependent. Infections and neutropenic fever only occurred in 10% and 4.5% of courses, respectively. There were no significant differences in pharmacokinetic parameters between schedules A and B. The dose levels docetaxel 100 mg/m^2 plus cisplatin 75 mg/m^2 or docetaxel 85 mg/m^2 plus cisplatin 100 mg/m^2 appeared to be manageable.

Chapter 4 involves a prospective study on the incidence of neuropathy induced by combination chemotherapy of docetaxel and cisplatin, two potentially neurotoxic drugs. In 29 of 55 patients (53%) a predominantly sensory neuropathy was reported. However, at cumulative doses over 200 mg/m^2 of both docetaxel and cisplatin, 26 out of 35 patients (74%) developed a neuropathy that was mild in 15, moderate in 10 and severe in 1. Combination chemotherapy of docetaxel and cisplatin induces a dose-dependent sensory neuropathy that is more severe than with the use of either docetaxel or cisplatin as a single agent at similar doses.

In *chapter 5* a phase I study is presented on docetaxel and ifosfamide in patients with advanced solid tumors. Treatment consisted of docetaxel given as a 1-hour infusion followed by ifosfamide as a 24-hour infusion (schedule A) or ifosfamide followed by docetaxel (schedule B) every 3 weeks. Docetaxel doses ranged from 60-85 mg/m^2 and ifosfamide doses from 2.5-5.0 g/m^2. A total of 34 patients were entered into this study. Granulocytopenia grade 3 and 4 was common (89%), short lasting and ifosfamide dose dependent. Febrile neutropenia and sepsis occurred in 17% and 2% of courses respectively. There

was no pharmacokinetic interaction between docetaxel and ifosfamide. A dose of 75 mg/m^2 of docetaxel followed by 5.0 g/m^2 of ifosfamide appeared to be manageable.

Chapter 6 describes a comparative study that was performed to investigate if the venotonic drug hydroxyethylrutosiden could reduce or delay docetaxel-related fluid retention. Eighty-five patients with metastatic breast cancer who were treated with docetaxel were allocated to receive either hydroxyethylrutosiden 300 mg given orally 4 times daily or no hydroxyethylrutosiden. Unfortunately, there was no difference in the development of fluid retention or weight gain between the two groups. We conclude that hydroxyethylrutosiden does not reduce or delay the incidence and severity of docetaxel-related fluid retention.

Chapter 7 presents a prospective study that was performed to determine if corticosteroid comedication reduces the incidence and severity of docetaxel-induced neuropathy. Two groups of patients treated with docetaxel were prospectively analyzed for neurotoxicity. Group A consisted of 38 patients with a variety of solid tumors who did not receive corticosteroid comedication, while group B consisted of 49 female patients with metastatic breast cancer who were treated with corticosteroid comedication. There was no statistically significant difference in neurotoxicity between group A and B. We conclude that corticosteroid comedication does not reduce the development of docetaxel-related neuropathy.

Conclusions and future perspective

Docetaxel is a new antimicrotubule agent that has proven activity in a variety of solid tumors. In the treatment of metastatic breast cancer docetaxel has shown to have great potential as first and second line chemotherapy. In 1995 the drug was registered for the treatment of advanced breast cancer. The role of docetaxel as first line (standard) chemotherapy in advanced breast cancer still has to be determined. In view of this, we are presently performing a

randomized phase II/III study of doxorubicin and docetaxel versus fluorouracil, doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer.

The antitumor activity in non-small cell lung cancer (NSCLC), head and neck cancer and soft tissue sarcoma in first and second line chemotherapy is very interesting, considering the generally disappointing response rates of chemotherapy for advanced disease in these tumor types. Several studies on docetaxel in combination with other antitumor agents are underway to determine their value for patients with these types of cancer. The schedules we developed with docetaxel/cisplatin and docetaxel/ifosfamide are currently being tested in phase II studies on NSCLC and phase III studies in head and neck cancer, and in phase II studies in NSCLC and breast cancer respectively.

More studies will have to be performed in an attempt to reduce the side effects of docetaxel. Especially the prevention and/or reduction of fluid retention and neurotoxicity, two frequent, usually mild but sometimes disabling toxicities at high cumulative doses of docetaxel, should be further investigated.

SAMENVATTING

In dit proefschrift worden klinische en farmacologische studies beschreven met docetaxel, een agens gericht tegen microtubuli, in combinatie met respectievelijk cisplatin en ifosfamide. De incidentie van neurotoxiciteit geïnduceerd door de combinatie van docetaxel met cisplatin én door docetaxel monotherapie werden prospectief onderzocht. Tevens werden studies verricht met het doel de door docetaxel geïnduceerde vochtretentie en neurotoxiciteit, twee frequente en soms invaliderende bijwerkingen, te reduceren dan wel uit te stellen.

In *hoofdstuk 1* wordt een inleiding gegeven over de ontwikkeling van een nieuwe groep medicijnen die gericht zijn tegen microtubuli, de taxanen. Deze ontwikkeling begon met de extractie van paclitaxel uit de bast van de Pacific Taxus Brevifolia aan het eind van de jaren 60. Dit werd gevolgd door de ontwikkeling van docetaxel, een semi-synthetisch analogon van paclitaxel, waarbij gebruik werd gemaakt van een precursor die geëxtraheerd werd uit de naalden van de Europese Taxus Baccata. Docetaxel bleek zeer actief te zijn bij de behandeling van verschillende solide tumoren.

Hoofdstuk 2 geeft een overzicht van de preklinische en klinische studies met enkelvoudig docetaxel, de ontwikkeling van combinaties van docetaxel met andere geneesmiddelen, en de bijwerkingen. In preklinische studies toonde docetaxel indrukwekkende cytotoxische activiteit. Fase I studies met docetaxel lieten zien dat de belangrijkste dosis limiterende bijwerking een kortdurende, cumulatieve neutropenie is die dosis afhankelijk is en niet gerelateerd aan het toedieningsschema. Andere bijwerkingen bleken meestal weinig ernstig en bestonden uit alopecia, misselijkheid, braken, mucositis, diarrhee, neurotoxiciteit, weinig frequente overgevoeligheidsreacties, vochtretentie en huid- en nagelafwijkingen. De aanbevolen dosis en toedieningswijze voor fase II studies was 100 mg/m^2, toegediend als een 1-uurs infuus in een cyclus van 3 weken. Docetaxel blijkt een zeer krachtig middel te zijn bij de behandeling van

het gemetastaseerde mammacarcinoom, zowel in 1e als 2e lijns chemotherapie.

Hoofdstuk 3 laat de resultaten zien van een fase 1 en farmacologische studie met docetaxel en cisplatin bij patienten met gemetastaseerde solide tumoren. Deze studie werd uitgevoerd om te bepalen of deze combinatie haalbaar was en om de maximaal tolereerbare dosis vast te stellen. Tevens werden de bijwerkingen nauwkeurig vastgelegd en werd bestudeerd of deze werden beïnvloed door de volgorde van toediening van de geneesmiddelen. In totaal werden 64 patienten behandeld met docetaxel toegediend als 1-uurs infuus, gevolgd door cisplatin toegediend als 3-uurs infuus (schema A) of met cisplatin gevolgd door docetaxel (schema B). De docetaxel doses varieerden van 55-100 mg/m^2 en de cisplatin doses van 50-100 mg/m^2. Leucocytopenie en neutropenie kwamen frequent voor (totaal 90%; graad 3 of 4 87%), bleken kortdurend te zijn en afhankelijk van de dosis docetaxel. Ondanks deze neutropenie, kwamen infecties en neutropene koorts respectievelijk in slechts 10% en 4,5% van de kuren voor. Er werden geen significante verschillen gezien in farmacokinetiek tussen schema A en B. De dosisniveau's docetaxel 100 mg/m^2 met cisplatin 75 mg/m^2 of docetaxel 85 mg/m^2 met cisplatinum 100 mg/m^2 bleken hanteerbaar te zijn.

Hoofdstuk 4 beschrijft een prospectieve studie naar de incidentie van neuropathie geinduceerd door combinatie chemotherapie met docetaxel en cisplatin, twee potentiele neurotoxische cytostatica. In 29 van de 55 evalueerbare patienten (53%) werd een voornamelijk sensibele neuropathie waargenomen. Echter bij cumulatieve doseringen boven de 200 mg/m^2 van zowel docetaxel als cisplatinum ontwikkelden 26 van de 35 patienten (74%) een neuropathie die gering was bij 15-, matig ernstig bij 10 patienten en ernstig bij 1 patient. Combinatie chemotherapie met docetaxel en cisplatinum induceert dus een dosis afhankelijke sensibele neuropathie die ernstiger is dan die geïnduceerd door enkelvoudig docetaxel of cisplatin in vergelijkbare doseringen.

In *hoofdstuk 5* wordt een fase 1 studie gepresenteerd met docetaxel en

ifosfamide bij patienten met gemetastaseerde solide tumoren. De behandeling bestond uit docetaxel toegediend als 1-uurs infuus gevolgd door ifosfamide als 24-uurs infuus (schema A), of ifosfamide gevolgd door docetaxel (schema B), elke 3 weken. Docetaxel doseringen varieerden van 60-85 mg/m^2 en ifosfamide doseringen van 2.5-5.0 g/m^2. In totaal werden 34 patienten behandeld. Granulocytopenie graad 3 en 4 kwamen veel voor (89%), waren kortdurend en bleken afhankelijk van de dosis ifosfamide. Febriele neutropenie en sepsis kwamen respectievelijk bij 17% en 2% van de kuren voor. Er was geen farmacokinetische interactie tussen docetaxel en ifosfamide. De combinatie docetaxel 75 mg/m^2 gevolgd door ifosfamide 5.0 g/m^2 blijkt hanteerbaar te zijn.

Hoofdstuk 6 beschrijft een vergelijkende studie die werd uitgevoerd om te onderzoeken of het venotonicum hydroxyethylrutosiden het ontstaan van docetaxel gerelateerde vochtretentie kan reduceren of uitstellen. Vijfentachtig patienten met gemetastaseerd mammacarcinoom die werden behandeld met docetaxel kregen óf hydroxyethylrutosiden voorgeschreven in een dosering van 4 maal daags 300 mg oraal of geen hydroxyethylrutosiden. Er was uiteindelijk geen verschil in het voorkomen van vochtretentie of gewichtstoename tussen de 2 groepen. Wij concluderen dat hydroxyethylrutosiden de incidentie noch de ernst van docetaxel gerelateerde vochtretentie beïnvloedt.

Hoofdstuk 7 omvat een prospectieve studie die werd uitgevoerd om na te gaan of comedicatie met corticosteroiden de incidentie en ernst van docetaxel-geïnduceerde neuropathie kan reduceren. Twee groepen patienten die werden behandeld met docetaxel werden niet gerandomizeerd prospectief geanalyseerd voor wat betreft neurotoxiciteit. Groep A bestond uit patienten met verschillende soorten solide tumoren die geen corticosteroiden toegediend kregen, terwijl groep B uit 49 vrouwelijk patienten met gemetastaseerd mammacarcinoom bestond die wel werden behandeld met corticosteroiden. Er was geen statistisch significant verschil in neurotoxiciteit tussen groep A en B. Blijkbaar beïnfvloedt comedicatie met corticosteroiden de ontwikkeling van docetaxel-gerelateerde neuropathie niet.

Conclusies en toekomst-perspectief

Docetaxel is een nieuw cytostatium, gericht tegen microtubuli, dat bewezen heeft effectief te zijn is bij de behandeling van diverse solide tumoren. Zo is docetaxel uiterst werkzaam bij de behandeling van het gemetastaseerde mammacarcinoom zowel in eerstelijns chemotherapie als in tweedelijns chemotherapie. In 1995 werd het geregisteerd voor de laatst genoemde indicatie. De precieze rol van docetaxel in de eerstelijns (standaard) chemotherapie van gemetastaseerd mammacarcinoom moet nog worden bepaald. In dit kader verrichten wij momenteel een gerandomizeerde fase 2/3 studie met doxorubicine en docetaxel versus fluorouracil, doxorubicine en cyclofosfamide.

De antitumor activiteit bij het niet-kleincellig longcarcinoom, hoofd-hals tumoren en weke delen sarcoom zowel in eerste als tweede lijns chemotherapie is interessant, gezien de veelal teleurstellende resultaten van chemotherapie bij de gemetastaseerde vormen van deze kankersoorten. Diverse studies met docetaxel in combinatie met andere cytostatica worden momenteel uitgevoerd om hun waarde voor patienten met deze vormen van kanker vast te stellen. Zo wordt het door ons ontwikkelde schema docetaxel/cisplatin momenteel bestudeerd in fase II studies bij niet-kleincellig bronchuscarcinoom en in fase III studie bij hoofd/hals tumoren. Het docetaxel/ifosfamide schema wordt toegepast in fase II studies bij longkanker en mammacarcinoom.

Verder onderzoek naar de bijwerkingen van docetaxel blijft noodzakelijk, zowel naar de pathogenese als naar de mogelijkheden deze bijwerkingen te verminderen of te voorkomen. Met name de preventie en/of reductie van vochtretentie en neurotoxiciteit, twee frequente, veelal milde maar soms invaliderende bijwerkingen bij hoge cumulatieve doseringen van docetaxel, moet verder worden onderzocht.

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CURRICULUM VITAE

Linda Christina Pronk werd op 24 april 1960 geboren te Nootdorp. In 1978 behaalde zij het diploma Gymnasium β aan het St. Stanislascollege te Delft, waarna zij in 1979 haar studie Geneeskunde begon aan de Erasmus Universiteit te Rotterdam. Tijdens haar studie verrichtte zij een keuzepracticum neuro-anatomie aan The National Institutes of Health, Bethesda, U.S.A. en doorliep zij de stages Haematologie en Gastroënterologie in het "Hospital de la Santa Cruz y San Pablo" te Barcelona, Spanje.

In juni 1986 werd het artsexamen afgelegd en meteen aangevangen met de opleiding Interne Geneeskunde in het Reinier de Graaf Gasthuis te Delft (opleider Dr. A.H. Mulder). Vanaf januari 1989 werd de opleiding tot internist vervolgd in het Zuiderziekenhuis te Rotterdam (opleider Prof.Dr. P.W. de Leeuw).

Per 1 juli 1991 begon zij haar werkzaamheden in de Dr. Daniel den Hoed Kliniek te Rotterdam, aanvankelijk als assistent geneeskundige in opleiding tot internist. De registratie als internist vond op 1 januari 1992 plaats waarna met de opleiding tot oncoloog werd begonnen. Sinds december 1994 is zij geregistreerd voor het aandachtsgebied oncologie.

Vanaf 1 januari 1998 zal zij werkzaam zijn als internist-oncoloog in het Universiteitziekenhuis "12 de Octubre" te Madrid, Spanje.