Docetaxel, ifosfamide and cisplatin in solid tumour treatment: a phase I study

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Docetaxel, ifosfamide and cisplatin have proven activity in a broad range of solid tumours and interfere with different phases of the cell cycle. We performed a phase I study with the aim to determine the maximum tolerated dose (MTD) of docetaxel, ifosfamide and cisplatin in patients with solid tumours and to define the safety, dose-limiting toxicity (DLT) and the recommended dose and administration schedule of docetaxel, ifosfamide and cisplatin for further phase II testing. Docetaxel was given by 1-h infusion on day 1, followed by ifosfamide 1000 mg/m^2/day as a continuous infusion for 5 days. Mesna was added at the same doses to the same infusion bag and was continued for 12 h after the end of ifosfamide. Cisplatin was administered as a 24-h infusion concomitantly with ifosfamide, but in separate infusion bags, either on day 5 (schedule A) or on day 1 (schedule B). Escalation steps were planned only for docetaxel (60, 75, 85 mg/m^2) and cisplatin (50, 75, 100 mg/m^2). No intrapatient dose escalation was permitted. Prophylactic ciprofloxacin was used after a protocol amendment was implemented. No prophylactic haematopoietic growth factors were used. Cycles of docetaxel, ifosfamide and cisplatin were given at 3-week intervals. Toxicity was scored according to National Cancer Institute Canada-Common Toxicity Criteria 2. The MTD was defined as the dose at which a DLT was observed in fewer than two of six patients during the first treatment cycle. In total, 85 patients received 309 cycles. Only three escalation steps could be explored and DLTs were observed at each dose level. In total, 32 patients and 49 cycles showed DLTs. Febrile neutropenia occurred in 20 patients (24%). Only two DLTs were nonhaematological (one cerebral infarction and one encephalopathy grade 4). Neutropenia grade 4 lasted for greater than 7 days and/or thrombocytopenia grade 4 was dose limiting in 10 patients. Febrile neutropenia occurred in five of 41 patients (12%) who received prophylactic ciprofloxacin and in 15 of 44 patients (34%) who did not. MTD was reached at level 3 (docetaxel, 75 mg/m^2 and cisplatin, 75 mg/m^2). With a lower dose of docetaxel (60 mg/m^2) both schedules A and B were feasible, although, overall, schedule A seemed to be better tolerated. On the basis of this phase I study, the recommended docetaxel, ifosfamide and cisplatin regimen is docetaxel (60 mg/m^2) on day 1, ifosfamide (1000 mg/m^2/day) on days 1–5 and cisplatin (75 mg/m^2) given on day 5. It is associated with substantial haematological toxicity, but this is feasible provided prophylactic antibiotics are used. *Anti-Cancer Drugs* **21:306–312 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2010, **21**:306–312

Keywords: cisplatin, docetaxel, ifosfamide, phase I

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Received 21 July 2009 **Revised form accepted** 26 October 2009

Introduction

Docetaxel is a semisynthetic taxane that interferes with the microtubule system, which consists of tubulin dimers and which is an essential component of the mitotic spindle and the cytoskeleton [1,2]. Docetaxel is active in multiple solid tumours including breast cancer, head and neck cancer, lung cancer, upper gastrointestinal cancer, bladder cancer, gynaecological malignancies and soft tissue sarcoma [3]. The pharmacokinetics of docetaxel as a single agent is linear [4]. Cisplatin reacts with the N7 position of purines to form a variety of DNA adducts. The cytotoxicity of cisplatin is associated with the arrest of the cells in the G_2 phase of the cell cycle [5–8]. Cisplatin is one of the most widely used cytotoxic drugs with activity in a wide variety of solid tumours including head and neck cancer, upper gastrointestinal cancer, bladder cancer, gynaecological malignancies, testicular cancer and lung cancer. Moreover, it is being used in the treatment of several paediatric tumours and tumours of the adolescent [5]. The free platinum concentration versus time data is best described by a biphasic curve. The α plasma half-life is 8 min and the β half-life is 35 min. Ifosfamide is an alkylating agent that needs metabolic activation by the liver microsomal P450-cytochrome system. Its main cytotoxic metabolite is isophospharamide mustard. The urotoxicity of acrolein, which is another metabolite, can be prevented by concomitant administration of mesna [9]. Ifosfamide is active in lung cancer, testicular cancer,

0959-4973 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e3283349994

breast cancer, gynaecological malignancies, gastric and pancreatic cancer, various types of lymphoma, soft tissue sarcoma, osteosarcoma and Ewing's sarcoma [9]. The pharmacokinetics of ifosfamide is nonlinear and is affected by dose and schedule of administration. Less than 20% of the drug is protein bound. It is mainly eliminated by metabolism and only 15–30% is excreted with the urine. The plasma half-life is 6 h [9]. Docetaxel at a dose of 75–100 mg/m^2 can be safely combined with cisplatin at a dose of 75–100 mg/m^2, both administered every 3 weeks [10,11]. Docetaxel (75 mg/m^2) has been combined with ifosfamide at a dose of 5 g/m^2 over 24 h [12]. The pharmacokinetics of docetaxel is independent of ifosfamide, but the pharmacokinetics of ifosfamide depends on the sequence of administration [13]. Cisplatin (100 mg/m^2) has been combined with ifosfamide at doses of 1000 mg/m^2/day, days 1–6, or 2000 mg/m^2, days 1–3 [14,15]. The toxicities of all these doublets were manageable. There is a rationale for combining all three drugs, docetaxel, ifosfamide and cisplatin, as these cytotoxic drugs have all proven activity in a broad range of solid tumours and, moreover, interfere at different phases of the cell cycle. However, the optimal sequence and dose of the three drugs so far had not been determined in a proper phase I trial at the time this study was started. In particular, the timing of cisplatin administration might be important as ifosfamide is known to decrease intracellular gluthatione levels in peripheral blood cells *in vivo* [16]. Intracellular gluthatione levels are correlated with cisplatin sensitivity [17,18].

Methods

Study design

This was a nonrandomized, open-label, single-centre phase I study of the three-drug combination of docetaxel, ifosfamide and cisplatin in patients with solid tumours.

Patients

Patients with a histologically confirmed advanced stage malignant solid tumour, which was either known to be sensitive to these agents or refractory to conventional effective therapy, or for whom no standard therapy existed, were eligible. Earlier chemotherapy and radiotherapy were allowed, provided they had been discontinued for more than 4 weeks. The required treatment-free interval was 6 weeks for earlier use of nitrosurea, mitomycin C and carboplatin, and 8 weeks if granulocyte-colony-stimulating factor (CSF) or granulocyte macrophage-CSF had been used. Other inclusion criteria were age above 18 years, performance status 0–2 according to the World Health Organization scale [19], life expectancy of greater than 12 weeks, and adequate organ function, defined as white blood cells greater than 4×10^9/l, absolute neutrophil count greater than 2×10^9/l, platelets greater than 100×10^9, serum creatinine less than 1.25 × upper normal limit, creatinine clearance greater than 60 ml/min, transaminases less than 3 × upper normal limit, alkaline phosphatase less than six times upper normal limit. Patients with a combination of an elevated transaminases level greater than 1.5 × upper normal limit and alkaline phophatase greater than 2.5 × upper normal limit, and with a history of significant neurological or psychiatric disorders, active infection, congestive heart failure, uncontrolled hypertension or serious arrhythmia requiring medication, known brain or leptomeningeal involvement, symptomatic peripheral neuropathy greater than two by National Cancer Institute Canada-Common Toxicity Criteria 2 [20], and earlier irradiation of more than 30% of bone marrow were excluded.

All patients provided written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Antwerp University Hospital.

Objectives

The primary objectives were to determine the maximum tolerated dose (MTD) of the combination of docetaxel, ifosfamide and cisplatin in two different administration schedules in cohorts of pretreated and untreated patients with solid tumours and to define the safety profile, dose-limiting toxicities and the recommended dose and schedule of the combination for further phase II testing.

Treatment schedule

Docetaxel was administered as a 1-h infusion on day 1, followed by ifosfamide (1000 mg/m^2/day) as a continuous infusion for 5 days. Mesna was added at the same doses to the same infusion bag and was continued for 12 h after the end of ifosfamide. Cisplatin was administered as a 24-h infusion concomitantly with ifosfamide, but in separate infusion bags, either on day 5 (schedule A) or on day 1 (schedule B). Methylprednisolone was administered orally 12 and 3 h before the docetaxel and every 12 h thereafter on days 1 and 2, for a total of six doses. An additional dose of methylprednisolone (125 mg) was given intravenously on day 1 and ondansetron (8 mg) was administered intravenously at a dose of 8 mg on days 1–5. Cycles were repeated every 3 weeks. At least two cycles were administered unless manifest disease progression, unacceptable toxicity or patient refusal occurred. The use of granulocyte-CSF or granulocyte macrophage-CSF was not permitted.

The next cycle was delayed until absolute neutrophil count recovered to greater than 1.5×10^9/l and the platelet count greater than 100×10^9/l. Patients went off study where there was a delay of more than 2 weeks. Cisplatin was withheld if neuropathy greater than grade 3 or creatinine clearance less than 40 ml/min or serum creatinine greater than 1.6 mg/dl occurred. The cisplatin dose was reduced to 50 mg/m^2 when serum creatinine was between 1.2 and 1.6 mg/dl or when the creatinine clearance was between 40 and 60 ml/min. Patients with

ifosfamide-induced encephalopathy were treated with methylene blue (50 mg) intravenously every 4 h until 72 h after the end of the ifosfamide infusion and methylene blue was administered prophylactically during the subsequent cycles at a dose of 50 mg four times a day commencing 4 h before the start of the ifosfamide infusion until 72 h after ending the infusion [21].

Definition of dose-limiting toxicity

Dose-limiting toxicity (DLT) was defined as (i) any grade 3 or 4 nonhaematological toxicity according to National Cancer Institute Canada-Common Toxicity Criteria 2, except for alopecia and fatigue and/or asthenia, (ii) grade 4 neutropenia for more than 7 days, (iii) febrile neutropenia (fever > 38.5 and absolute neutrophil count $< 0.5 \times 10^9$/l requiring hospitalization), (iv) thrombocytopenia grade 4, and (v) bleeding episode requiring platelet transfusion.

Dose escalation schedule, protocol amendments and maximum tolerated dose

No intrapatient dose escalation was permitted. The planned dose escalation schedule for docetaxel and cisplatin is shown in Table 1. The protocol was amended in May 2001, allowing the administration of prophylactic ciprofloxacin (2×500 mg/day) on days 5–15 of each cycle. Each dose level was tested with and without prophylactic antibiotic use. A second major amendment was introduced in April 2004. At that time, a dose level 2a was introduced, which combined docetaxel (60 mg/m^2) and cisplatin (75 mg/m^2). The ifosfamide dose remained unchanged at 1000 mg/m^2/day, days 1–5.

Three patients were to be included at each dose level. If one of three patients developed a DLT in the first treatment cycle, three more patients were to be treated at the same dose level. The MTD was defined as the dose at which a DLT was observed during the first treatment cycle in more than two patients [22]. Once the MTD was reached in schedule A, schedule B was started at one dose level below.

Assessments

The evaluation of side effects was based on weekly medical history and physical examination, and weekly complete blood counts and differential blood counts. Before each cycle, we also performed a serum analysis including sodium, potassium, calcium, creatinine, blood urea nitrogen, uric acid, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, lactate dehydrogenase, bilirubin, glucose, and albumin. Measurable or evaluable disease was not an inclusion criterion. However, patients with measurable disease were evaluated for response according to the World Health Organization criteria [23], before each cycle when the tumour was measurable by physical examination and before every other cycle when computed tomography or magnetic resonance imaging was needed for response evaluation. Patients who received more than two cycles were considered evaluable for response.

Table 1 Dose escalation schedule

Dose level	Docetaxel (mg/m^2)	Ifosfamide (mg/m^2/day × 5)	Cisplatin (mg/m^2)
1	60	1000	50
2	75	1000	50
3	75	1000	75
2a[a]	60	1000	75
4	85	1000	75
5	85	1000	100

[a]Protocol amendment.

Results

Eighty-five patients were enrolled between May 2000 and October 2004. Patient characteristics are summarized in Table 2. Three hundred and nine cycles were administered, with a median of four cycles per patient (range 1–7). Forty-one patients received prophylactic ciprofloxacin. Initially, at some dose levels, all patients were chemo-naive, which made the applicability of the results in pretreated patients questionable. We therefore added additional pretreated patients at these respective dose levels, which explains the higher number of patients as required by the protocol at some levels. Fifty-three cycles were delayed and a dose reduction was required in 23 cycles. The overall relative dose intensity for all patients receiving at least two cycles was over 90% for

Table 2 Patient characteristics

Characteristic	*N*
Median age (range), in years	57 (29–71)
WHO performance status	
0	13
1	63
2	8
3	1
Male/female	54/31
Tumour type	
Head and neck cancer	32
Ovarian cancer	6
Malignant melanoma	5
Stomach cancer	5
Pancreatic cancer	4
Oesophageal cancer	4
Neuroendocrine tumour	3
Lung cancer	4
Soft tissue sarcoma	3
Prostate cancer	3
Cervical cancer	2
Cancer of the vagina or vulva	2
Breast	2
Unknown primary	3
Other	7[a]
Earlier treatment	
None	25
Chemotherapy	38
Radiotherapy	30
Surgery	47

N, number of patients.
[a]Adrenocortical cancer, thyroid cancer, cancer of the small intestine, testicular cancer, osteosarcoma, hepatocellular carcinoma, cancer of the ear: each 1.

each of the three agents at all dose levels, both for schedule A and schedule B. Relative dose intensity was more than 90% in each of the first five cycles. The relative dose intensity in the sixth cycle, which was administered to 19 patients, was 83% for ifosfamide and docetaxel and 57% for cisplatin. Toxicities are shown in Table 3. Grade 4 neutropenia occurred in 181 cycles (59%) and in 68 patients (80%). The incidence of the observed dose-limiting toxicities is summarized in Tables 4 and 5. The incidence of DLTs was not different between the chemo-naive and pretreated patient cohorts. DLTs during the first cycle were observed in 22 patients. Only two of these DLTs were nonhaematological (one cerebral infarction and one encephalopathy grade 4). Febrile neutropenia occurred in 14 patients during the first cycle. Neutropenia lasting more than 7 days and grade 4 thrombocytopenia during the first treatment cycle were observed in six and two patients, respectively. Overall, DLTs were observed in 32 patients (38%) and in 49 cycles (16%). Nine patients had DLTs in two or more cycles. Febrile neutropenia occurred in 20 patients, in 28 cycles. Neutropenia grade 4 lasting more than 7 days was observed in 13 patients and in 19 cycles. Grade 4 thrombocytopenia occurred in three patients, in four cycles. Four patients had two DLT defining events simultaneously in the same cycle. Febrile neutropenia occurred in five of 41 patients (12%) who received prophylactic ciprofloxacin and in 15 of 44 patients (34%) who did not (Fisher's exact test, two-sided $P = 0.022$). With the use of prophylactic ciprofloxacin, level 2 DLT data

Table 3 Toxicities

	Percentage of cycles ($n=309$)				Percentage of patients ($n=85$)			
	Grade				Grade			
Toxicity	1	2	3	4	1	2	3	4
Haematological								
Neutropenia	5	6	16	59	2	4	8	80
Leukopenia	6	15	25	45	2	5	27	62
Thrombocytopenia	28	8	13	<1	29	12	27	2
Anaemia	39	53	6	<1	12	66	19	2
Nonhaematological								
Febrile neutropenia			8	1[a]			20	4[a]
Infection	2	1	4	<1[a]	4	4	14	1[a]
Nausea	26	11	3		22	24	8	
Vomiting	19	7	1	1	28	18	4	2
Anorexia	29	14	1	7	33	41	4	14
Constipation	13	5	<1	<1	28	11	1	1
Diarrhoea	11	3	1		22	6	4	
Stomatitis	12	1			25	4		
Alopoecia	14	66			12	76		
Skin	3	1			8	4		
Nail changes	4				12			
Peripheral neuropathy	14	4	2		29	8	6	
Encephalopathy	4	1	<1	<1	11	4	1	1
Oedema	7	1			18	1		
Pulmonary	4	9	2	1	12	12	4	4
Fatigue	52	22	6	<1	38	38	15	1

[a]Also 1 case of grade 5.

Table 4 Dose-limiting toxicities

	All patients		Without ciprofloxacin				With ciprofloxacin			
	Any cycle		Cycle 1		All cycles		Cycle 1		All cycles	
Dose level and schedule	*N*	*n*	*N*	n^a	N^b	n^b	*N*	n^a	N^b	n^c
Schedule A										
1	13	3	7	1	22	4	6	0	22	0
2	18	3	10	3	41	3	8	0	32	0
3	11	7	4	1	12	3	7	3	30	13
2a	15	7	6	3	22	7	9	1	29	2
Schedule B										
1	6	1	6	1	20	3	0		0	
2	14	7	6	3	18	4	8	4	31	4
2a	8	4	5	2	21	5	3	0	9	1
All patients	85	32	44	14	156	29	41	8	153	20

DLT, dose-limiting toxicity; *N*, number of patients; *n*, number of patients with DLT in any cycle.
[a]Number of patients with DLT in cycle 1.
[b]Number of administered cycles.
[c]Number of cycles with DLT.

Table 5 DLT type by dose level and schedule

Dose level AB±	*N* total	*n* total	Febrile neutropenia *N* Cycle 1	Febrile neutropenia *N* All cycles	Febrile neutropenia *n*	ANC >7 *N* Cycle 1	ANC >7 *N* All cycles	ANC >7 *n*	Thrombocytopenia *N* Cycle 1	Thrombocytopenia *N* All cycles	Thrombocytopenia *n*	Nonhaematological *N/n*
Schedule A												
Without AB												
1	7	22	1	3[a]	3	0	1	2	0	1	1	0
2	10	41	1	1	1	2	2	2	0	0	0	0
3	4	12	0	1	1	1	2	2	0	0	0	0
2a	6	22	2	4	6	0	0	0	0	0	0	1
With AB												
1	6	22	0	0	0	0	0	0	0	0	0	0
2	8	32	0	0	0	0	0	0	0	0	0	0
3	7	30	0	0	0	3[b]	5[b]	10	1	1	2	0
2a	9	29	0	0	0	0	1	1	0	0	0	1
Schedule B												
Without AB												
1	6	20	1	1	3	0	0	0	0	0	0	0
2	6	18	3	3	4	0	0	0	0	0	0	0
2a	5	21	2	2	4	0	1	1	0	0	0	0
With AB												
2	8	31	4[b]	4[b]	5	0	1	1	1	1	1	0
2a	3	9	0	1	1	0	0	0	0	0	0	0
Total	85	309	14	20	28	6	13	19	2	3	4	2

AB, prophylactic antibiotics (ciprofloxacin); ANC, absolute neutrophil count; ANC >7, neutropenia grade 4 for >7 days; DLT, dose-limiting toxicity; *N*, number of patients; *n*, number of cycles.
[a]Including one patient with ANC >7 and one patient with thrombocytopenia grade 4, both in one cycle.
[b]Including one patient with thrombocytopenia in one cycle.

(0/8 in A, 4/8 in B during the first cycle) suggest that regimen A was better tolerated. This was supported by the data of all patients at that dose level [3/18 (16.6%) in A vs. 7/14 (50%) in B] (Fisher's exact test, two-sided $P = 0.062$). However, with a lower dose of docetaxel (60 mg/m^2) and the higher dose of cisplatin (75 mg/m^2), the tolerance to the A and B schedule appeared more or less comparable. We observed 36 objective tumour responses (29), partial responses, and seven complete responses in patients with squamous cell carcinoma of the head and neck (22), non-small-cell lung cancer (3), leiomyosarcoma (2), pancreatic cancer (1), ovarian cancer (1), carcinoma of the vagina (1), gastric cancer (1), testicular cancer (1), cervical cancer (1), oesophageal cancer (1), neuroendocrine tumour (1) and an unknown primary (1).

Discussion

The combination of ifosfamide (1000 mg/m^2/day) on days 1–5 with docetaxel and cisplatin was associated with a high incidence of haematological toxicity, even at the initial dose level that used docetaxel (60 mg/m^2) and cisplatin (50 mg/m^2). The incidence of febrile neutropenia in the entire study population (24%) exceeded the commonly recommended 20% threshold for prophylactic use of granulocyte-CSF [24–26]. However, the incidence of febrile neutropenia was significantly lower (12%) with the prophylactic use of antibiotics, that is, ciprofloxacin (500 mg bid) day 5–15 of each 3-week cycle. This is in line with the results of randomized phase III trials, which have shown the usefulness of the prophylactic use of antibiotics in the prevention of febrile neutropenia [27,28].

Our study at least suggests that schedule A was better tolerated. Indeed, the combinations of docetaxel 75 mg/m^2/cisplatin 50 mg/m^2 (level 2) and docetaxel 60 mg/m^2/cisplatin 75 mg/m^2 (level 2a) were both feasible for schedule A, provided prophylactic antibiotics were used. In contrast, dose level 2 was already unacceptably toxic with schedule B, whether prophylactic antibiotics were used or not. However, dose level 2a was also tolerated by patients receiving the B schedule when prophylactic antibiotics were used. Considering the fact that the DLTs were mainly determined by neutropenia (and to a lesser extent by thrombocytopenia), this points to the crucial role of the docetaxel dose in this triple regimen. Table 6 summarizes the published data on docetaxel, ifosfamide and cisplatin combinations. Neutropenia was the dominant and DLT in all these studies, irrespective of the schedule of ifosfamide and cisplatin [29–32].

Intracellular glutathione levels are correlated with cisplatin resistance. Mechanisms involved include binding and inactivating cisplatin, enhancing DNA repair, and reducing cisplatin-induced oxidative stress [17,18]. This effect of intracellular glutathione levels on resistance to cisplatin seems to be unrelated to the formation of platinum–DNA adducts [18]. Ifosfamide is known to decrease intracellular glutathione levels in head and neck cancer, ovarian cancer, breast cancer, and murine leukaemia cell lines *in vitro*, and in peripheral blood

Table 6 Published studies on the DIP combination

Author	Tumour type	*N*	Chemo-naive patients	Dose			Treatment interval	G-CSF support[a]	Grade 4 neutropenia (%)	FN %
				Docetaxel	Ifosfamide	Cisplatin				
Kunitoh *et al.* [29]	Lung cancer	33	33	60 mg/m^2, day 1	700–2000 mg/m^2/day, days 2–4[d]	60 mg/m^2, day 1	21–28 days	Therapeutic	NR	NR
Kosmas *et al.* [30]	Lung	55	55	80–100 mg/m^2 day 1[c]	2000–2500 mg/m^2/day, days 1–2	40–50 mg/m^2/day, days 1–2	21 days	Prophylactic	57	20
Takahashi *et al.* [31]	Metastatic urothelial cancer	14	9	60 mg/m^2, day 1	1000 mg/m^2/day, days 2–6	20 mg/m^2/day, days 2–6	21 days	No	36	21
Recchia *et al.* [32]	Head and neck cancer	24	24	40–70 mg/m^2 day 1[b]	1200 mg/m^2/day, days 1–4	20 mg/m^2/day, days 1–4	28 days	No	34	20
This series	Solid tumours	85	47	50–75 mg/m^2, day 1	1000 mg/m^2/day, days 1–5	50–75 mg/m^2 days 1 or 5	21 days	No	80	24

FN, febrile neutropenia; DIP, docetaxel, ifosfamide and cisplatin; G-CSF, granulocyte-colony-stimulating factor; *N*, number of patients; MTD, maximum tolerated dose; NR, not reported.
[a]Prophylactic antibiotics were only used in this series (in 41/85 patients).
[b]MTD of docetaxel was determined at 70 mg/m^2.
[c]MTD was determined at docetaxel 100 mg/m^2, ifosfamide 2500 mg/m^2/day, days 1–2 and cisplatin 40 mg/m^2/day, days 1–2.
[d]MTD of ifosfamide was determined at 1500 mg/m^2/day, days 2–4.

cells *in vivo*, particularly when ifosfamide and mesna are administered over several days [16,33–38]. At least theoretically, schedule A with cisplatin administered on day 5, could potentially enhance cisplatin sensitivity by decreasing intracellular glutathione levels at the time when cisplatin is administered.

In conclusion, our study showed that a triple regimen of docetaxel (60 mg/m^2) on day 1, 5 days of ifosfamide (1000 mg/m^2/day), and cisplatin (75 mg/m^2) is feasible, without the use of growth factors, provided prophylactic antibiotics are used. However, its use is associated with substantial haematological toxicity. Our study suggests that the schedule with cisplatin administered on day 5 is better tolerated and is therefore recommended for further phase II testing.

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