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Comparison of Paclitaxel and Docetaxel Activity on Human Ovarian Carcinoma Xenografts

M.I. Nicoletti, V. Lucchini, M. D'Incalci and R. Giavazzi

The antitumour activity of paclitaxel (NSC 125973) and docetaxel (RP 56976, NSC 628503) was evaluated and compared against human ovarian carcinoma (HOC) xenografts in nude mice. Paclitaxel and docetaxel were given intravenously (i.v.) at a dose range of 16.6–34.5 mg/kg, once every 4 days for three consecutive doses to nude mice with HOC xenografts, transplanted subcutaneously (s.c.) (HOC18 and HOC22-S) or intraperitoneally (i.p.) (HOC8 and HOC22). Paclitaxel and docetaxel, at the highest dosage, induced complete tumour regression in 80–100% and 67% of mice bearing HOC22-S and HOC18 s.c., respectively. Both drugs cured 100% of mice bearing early stage HOC22 tumour in the peritoneal cavity, while treatment at an advanced stage significantly increased the survival time of all the mice. Both induced a 57% cure rate in mice bearing HOC8 in the peritoneal cavity. Paclitaxel and docetaxel were more effective than cisplatin (4 mg/kg, same dosing regime as above) used as a reference compound. These findings indicate that paclitaxel and docetaxel were highly active on four HOC xenograft models. No significant difference between them was detected in ovarian cancer xenografts.

Key words: human ovarian carcinoma, nude mice, paclitaxel, docetaxel
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INTRODUCTION

PACLITAXEL IS one of the most promising antineoplastic drugs to have been developed in the past few years [1, 2]. This antimitotic agent is isolated from the bark of the Pacific yew *Taxus brevifolia*, which acts by promoting the assembly of microtubules even in the presence of calcium chloride and at low temperatures, conditions that normally induce tubulin depolymerisation [3]. This action, different from the other spindle poisons, endows the compound with a unique mechanism of action. Paclitaxel had a broad spectrum of activity in preclinical studies against murine tumours and human xenografts [4–6]. In clinical trials, paclitaxel has proved effective against a variety of solid tumours such as melanoma, ovarian, breast and non-small cell lung carcinomas and leukaemias [7–14].

Major problems in the fast development of paclitaxel have been the lack of an adequate supply of this scarce natural product, together with its structural complexity, that makes synthesis problematic [1].

Docetaxel, a semisynthetic compound structurally related to paclitaxel, represents an interesting option [15, 16]. Its precursor, 10-deacetyl baccatin III, is obtained from the needles of *Taxus baccata*, then esterified with a synthetic side-chain, providing a renewable source of a natural product. Docetaxel, like paclitaxel, is a spindle poison. Docetaxel is slightly more potent than paclitaxel as a promoter of tubulin polymerisation [17, 18], and is twice as potent as an inhibitor of microtubules depolymerisation [15]. *In vitro*, docetaxel has greater cytotoxic potency than paclitaxel [17, 19–21].

Docetaxel has activity *in vivo* against a variety of early and advanced murine tumours [16], and has also shown activity against human xenograft models [22, 23]. Phase I trials have indicated some clinical response [24–27], and current phase II trials indicate very promising results in breast, ovary and non-small cell lung cancer [28–30]. At present, several clinical trials with paclitaxel and docetaxel are ongoing, but any comparison of the two drugs' toxic and antitumour effects would be premature as it requires extensive examination with a large number of patients.

Because paclitaxel's earlier trials showed particularly encouraging activity against refractory ovarian carcinomas [9, 14], trials with paclitaxel and docetaxel have tended to enroll patients with this neoplasia. Therefore, human ovarian carcinoma (HOC) xenografts in nude mice are a representative preclinical model. We recently found that paclitaxel was highly active against two malignant HOC transplanted in the peritoneal cavity of nude mice [6]. In this study, we compared the activity of paclitaxel and docetaxel against four human ovarian carcinoma xenograft models.

MATERIALS AND METHODS

Animals

Female NCr nu/nu mice were obtained from the Division of Cancer Treatment, NCI Animal Production Colony (Frederick, Maryland, U.S.A.), and were used when 8–10 weeks old and

Correspondence to R. Giavazzi.
M.I. Nicoletti and R. Giavazzi are at the Istituto di Ricerche Farmacologiche 'Mario Negri', Via Gavazzeni 11, 24125 Bergamo; V. Lucchini is at the Anatomia Patologica, Ospedale San Gerardo, Via Solferino, Monza; and M. D'Incalci is at the Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea 62, 20157 Milan, Italy.
Procedures involving animals and their care are conducted in conformity with the institutional guidelines that are in compliance with national and international laws and policies (EEC council directive 86/609, OJL 358, 1, Dec. 12, 1987; NIH guide for the care and use of laboratory animals, NIH publication no. 85-23, 1985).
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with a weight of 23 ± 2 g. The mice were housed in air-filtered laminar flow cabinets and manipulated according to aseptic procedures.

Tumour lines

HOC18, HOC8 and HOC22 are poorly differentiated serous adenocarcinomas of the ovary, and were derived respectively from a primary tumour, a pleural effusion and ascites of three different patients. These tumour lines were established and maintained in nude mice as described previously [31]. Routinely HOC18 was maintained subcutaneously (s.c.) and HOC8 and HOC22 intraperitoneally (i.p.) in nude mice. HOC22-S was derived from HOC22 transplanted s.c. HOC xenografts were used between passage 8–12 in nude mice.

Drugs

Paclitaxel (Bristol Myers Squibb, Wallingford, Connecticut, U.S.A.) was provided by the Developmental Therapeutic Program, Division of Cancer Treatment, NCI (U.S.A.), docetaxel through the kindness of Dr M.C. Bissery (Rhône-Poulenc Rorer S.A., Vitry-sur-Seine, France) and cisplatin (DDP) by Bristol Myers Squibb.

Paclitaxel was dissolved in a vehicle containing 50% polyoxyethylated castor oil (Cremophor EL) and 50% ethanol, and further diluted with 5% glucose in water. Docetaxel was first dissolved in ethanol, then 1 volume of solution was mixed with 1 volume of polysorbate 80, and diluted to the final concentration with glucose 5% in water. DDP was dissolved in 0.9% NaCl.

Drug treatment

HOC18 was implanted s.c. as 2–3 mm tumour fragments in the flanks of nude mice, and HOC22-S was implanted s.c. as a 10^7 cell suspension. HOC8 and HOC22 were injected i.p. as a 10^7 ascites-derived cell suspension. They grew in the peritoneal cavity producing ascites and infiltration of the peritoneal organs [31]. Before distribution to the various treatments, animals were randomised, on the basis of body weight for i.p. tumours, and tumour size for s.c. tumours.

For s.c. growing tumours, treatment started when all mice had a palpable growing tumour (approximately 5 mm in diameter).

For i.p. growing tumours, treatment started 3 days (early stage) and 15 days (advanced stage) after tumour transplant. The presence of tumour in the peritoneal cavity at the beginning of treatment was confirmed by cytohistological analysis of three additional mice per group as described previously [6].

Paclitaxel and docetaxel were given intravenously (i.v.) (0.2 ml per injection) once every 4 days, with three consecutive doses given over 9 days, at the doses specified in the Results. DDP was given i.v. with the same schedule at the maximum tolerated dose of 4 mg/kg.

Evaluation of the therapeutic response

Mice were weighed three times a week to evaluate drug-induced toxicity. Body weight changes, including tumour weight, were recorded. The maximum body weight loss after treatment was reported.

Subcutaneous growth. The diameters of the tumours were measured twice a week in two dimensions with a caliper. The end-point of the experiments was when tumours reached ≥1.5 g or 60 days after treatment. Tumour weight was calculated from the formula:

$$\text{Tumour weight (mg)} = \frac{(\text{length} \times \text{width})^2}{2}$$

Tumour regressions were assessed at the day of maximum tumour growth inhibition. A complete response corresponds to tumour regression below the limit of palpation, and a partial response corresponds to greater than a 50% reduction in tumour mass. Cured indicates mice without tumour 60 days after treatment.

Intraperitoneal growth. Mice were monitored twice a week for the presence of the tumour in the peritoneal cavity (abdominal distension), and body weight changes were recorded. The end-point used for assessing activity was an increase in lifespan (%ILS), determined as:

$$\frac{(\text{Median survival day of treated group} - \text{median survival day of control group})}{\text{Median survival day of control group}} \times 100$$

At autopsy, the peritoneal cavity was macroscopically examined to ascertain the presence of tumour. Differences in survival times were analysed by the log-rank test. If treated mice presented no gross evidence of growing tumour in the peritoneal cavity, they were killed and necropsied 90 days after the death of the last control animal. The absence of tumour in cured mice was confirmed by cytohistological examination [6]. Routinely, ovaries, pancreas, spleen, liver, omentum, diaphragm, lung and samples of lymph nodes were analysed by standard histological techniques; cell suspensions from the peritoneal lavage were cytocentrifuged, fixed and stained according to Papanicolaou.

RESULTS

Effects of paclitaxel and docetaxel against s.c. growing HOC xenografts

Tables 1 and 2 show the antitumour activity of paclitaxel and docetaxel on HOC22-S and HOC18 growing s.c. in the flanks of nude mice. Treatment started when all mice had a palpable growing tumour. Drugs were administered i.v. at doses ranging from 16.6 to 34.5 mg/kg/injection.

HOC22-S (*Table* 1). Paclitaxel and docetaxel at the lowest dose tested of 16.6 mg/kg induced partial responses but no cures. At higher dosages, both drugs were highly active with no significant difference between them. Complete tumour responses were seen in mice receiving 20–34.5 mg/kg paclitaxel or docetaxel. However, at these dosages, docetaxel was more toxic than paclitaxel, as shown by body weight loss. DDP was also active at the dose (4 mg/kg) tested. Complete regressions were maintained 60 days after treatment when the experiment was terminated.

HOC18 (*Table* 2). Paclitaxel and docetaxel were highly active on HOC18 growing s.c. at all dosages tested. At the highest concentration of 34.5 mg/kg, both drugs induced complete regression, resulting in 67% cured tumours 60 days after treatment. At the lower dosages (16.6–20 mg/kg) docetaxel seemed more active than paclitaxel, producing more complete responses. However, 60 days after treatment, two mice receiving paclitaxel were still tumour free, as was one mouse treated with docetaxel. Moreover, at equitoxic dosages, for example, 20 mg/kg for docetaxel and 34.5 mg/kg for paclitaxel (respectively, 9 and 10% body weight loss), paclitaxel was slightly more active than docetaxel. DDP at an equitoxic dose (4 mg/kg, 8% body weight loss) showed less activity than paclitaxel and docetaxel, with no mice cured.

Table 1. Effect of paclitaxel and docetaxel on HOC22-S growing subcutaneously in nude mice

Treatment* (i.v.)	Dose (mg/kg/injection)	Schedule days	Toxic deaths (day)	% of mean body weight† loss (day of nadir)	Tumour regressions (day 40)‡		Cured§
					Partial	Complete	
Control	–	12,16,20	0/6	–	0/6	0/6	0/6
Paclitaxel	16.6	12,16,20	0/5	–	5/5	0/5	0/5
	20.0		0/5	–	2/5	3/5	2/5
	28.8		0/6	3% (22)	1/6	5/6	5/6
	34.5		1/6 (21)	2.4% (22)	1/5	4/5	4/5
Docetaxel	16.6	12,16,20	0/6	6% (25)	4/6	0/6	0/6
	20.0		0/6	5% (22)	3/6	2/6	2/6
	28.8		1/6 (20)	17% (25)	2/5	3/5	2/5
	34.5		0/6	16% (22)	0/6	6/6	6/6
Cisplatin	4	12,16,20	0/5	2% (25)	2/5	3/5	3/5

* HOC22-S was injected subcutaneously, and intravenous (i.v.) drug treatment started after 12 days when all mice had a palpable growing tumour (5 ± 2 mm in diameter). † Average mouse weight at the beginning of treatment: 24.2 ± 0.8 g. ‡ Control tumours at day 40 = 441 ± 159 mg. The partial regression column does not include complete regressions. § Cured mice 60 days after treatment.

Table 2. Effect of paclitaxel and docetaxel on HOC18 growing subcutaneously in nude mice

Treatment* (i.v.)	Dose (mg/kg/injection)	Schedule days	Toxic deaths (day)	% of mean body weight† loss (day of nadir)	Tumour regressions (day 59)‡		Cured§
					Partial	Complete	
Control	–	31,35,39	0/6	–	0/6	0/6	0/6
Paclitaxel	16.6	31,35,39	0/7	–	2/7	1/7	0/7
	20.0		0/7	–	3/7	2/7	2/7
	34.5		0/6	10% (43)	0/6	6/6	4/6
Docetaxel	16.6	31,35,39	0/7	9% (46)	3/7	4/7	1/7
	20.0		0/6	9% (46)	2/6	4/6	0/6
	34.5		1/7 (43)	16% (49)	0/6	6/6	4/6
Cisplatin	4	31,35,39	0/7	8% (46)	3/7	0/7	0/7

* HOC18 was injected subcutaneously, and intravenous (i.v.) drug treatment started after 31 days when all mice had a palpable growing tumour (5 mm ± 2 in diameter). † Average mouse weight at the beginning of treatment: 24.2 ± 0.6 g. ‡ Control tumours at day 59 = 612 ± 210 mg. The partial regression column does not include complete regressions. § Cured mice 60 days after treatment.

Effects of paclitaxel and docetaxel against HOC xenografts growing in the peritoneal cavity

In patients, ovarian carcinomas disseminate in the peritoneal cavity and produce ascites. Therefore, HOC xenografts that grow in the peritoneal cavity of nude mice and form ascites and disseminating tumours mimic clinical disease well [31], and offer an ideal model for studying treatments for this neoplasia. The antitumour activity of paclitaxel and docetaxel was assayed on two human ovarian carcinoma xenografts (HOC8 and HOC22) transplanted i.p. in nude mice (Tables 3–5). In these studies, the mean body weight losses were 0, 2, 9% and 4, 7, 14%, respectively, for paclitaxel and docetaxel at doses of 16.6, 20 and 34.5 mg/kg/injection, and 12% for DDP at 4 mg/kg/injection.

HOC8 (*Table 3*). Paclitaxel and docetaxel treatment started 3 days after the transplant of HOC8 i.p., when all mice presented tumour cells in the peritoneal lavage and small tumour deposits on the omentum [6]. Paclitaxel and docetaxel delayed tumour growth and increased the survival time of all mice. At the highest dose tested (34.5 mg/kg), both were highly active and all mice had no visible tumour burden 32 weeks after transplant. Post-mortem microscopic analysis showed no evidence of tumours in four of seven mice for each group (57% cured). Two mice treated with docetaxel showed metastases to the omentum and one to the pancreas, and two mice treated with paclitaxel presented metastases to the omentum and one to the diaphragm. One toxic death occurred with paclitaxel on day 12 and one with docetaxel on day 13. Paclitaxel at 20 mg/kg induced an ILS of 140% ($P < 0.001$) with two cures, while docetaxel at the same dose produced an ILS of 129% ($P < 0.005$) with no cures. The absence of tumour in the two survivors was confirmed by cytohistological analysis.

DDP, 4 mg/kg/injection, was less active than paclitaxel and docetaxel on HOC8, with an ILS of 66% ($P < 0.01$) and no cures. One toxic death occurred with DDP on day 17.

Table 3. Effect of paclitaxel and docetaxel on early stage HOC8 growing in the peritoneal cavity of nude mice

Treatment* (i.v.)	Dose (mg/kg/injection)	Schedule days	Toxic deaths (day)	MST† (days)	Response %ILS	Survival‡	Cured§
Control	–	3,7,11	0/16	73 (49–134)	–	0/16	0/16
Paclitaxel	20	3,7,11	0/8	162 (109–197)‖	140	2/8	2/8
	34.5		1/8 (12)	n.e.	n.e.	7/8	4/7
Docetaxel	20	3,7,11	0/8	190 (63–288)¶	129	0/8	0/8
	34.5		1/8 (13)	n.e.	n.e.	7/8	4/7
Cisplatin	4	3,7,11	1/8 (17)	120 (96–190)**	66	0/8	0/7

* HOC8 was injected intraperitoneally, and intravenous (i.v.) drug treatment started after 3 days. † Median survival time with range. Surviving mice are not included. ‡ Number of mice alive on day 224. § Tumour-free mice on day 224. ‖ $P \leq 0.001$. ¶ $P \leq 0.005$. ** $P \leq 0.01$. n.e., non-evaluable; ILS, increase in life span.

Table 4. Effect of paclitaxel and docetaxel on early stage HOC22 growing in the peritoneal cavity of nude mice

Treatment* (i.v.)	Dose (mg/kg/injection)	Schedule days	Toxic deaths (day)	Response %ILS†	Survival‡	Cured§
Control	–	3,7,11	0/16	–	0/16	0/16
Paclitaxel	16.6	3,7,11	0/8	136	5/8	4/8
	20		0/8	n.e.	8/8	7/8
	34.5		1/8 (9)	n.e.	7/8	7/7
Docetaxel	16.6	3,7,11	0/8	n.e.	6/8	6/8
	20		0/8	n.e.	8/8	5/8
	34.5		0/7	n.e.	7/7	7/7
Cisplatin	4	3,7,11	1/8 (15)	126	0/8	0/8

* HOC22 was injected intraperitoneally, and intravenous (i.v.) drug treatment started after 3 days. † Surviving mice are not included. Median survival day in control group 63.5 (range 42–83). ‡ Number of mice alive on day 180. § Tumour-free mice on day 180. n.e., non-evaluable.

Table 5. Effect of paclitaxel and docetaxel on late stage HOC22 growing in the peritoneal cavity of nude mice

Treatment* (i.v.)	Dose (mg/kg/injection)	Schedule days	Toxic deaths (day)	MST† (days)	Response %ILS	Survival‡
Control	–	14,18,22	0/8	45 (24–60)	–	0/8
Paclitaxel	20	14,18,22	0/8	142 (85–236)§	216	0/8
	34.5		0/8	192 (147–280)§	326	0/8
Docetaxel	20	14,18,22	0/8	178 (77–205)§	295	0/8
	34.5		0/8	245 (122–267)§	444	0/8
Cisplatin	4	14,18,22	1/8 (15)	88.5 (84–98)‖	97	0/8

* HOC22 was injected intraperitoneally, and intravenous (i.v.) drug treatment started after 15 days. † Median survival time with range. ‡ Number of mice alive on day 280. § $P \leq 0.001$. ‖ $P \leq 0.05$.

HOC22 (*Tables* 4, 5). Paclitaxel and docetaxel were given i.v. to nude mice bearing early (3 days after i.p. transplant) and advanced (15 days after i.p. transplant) HOC22 in the peritoneal cavity. Three days after the transplant of HOC22 i.p., mice presented tumour cells in the peritoneal lavage and microscopic tumour deposits; 15 days later all mice developed ascites and extensive involvement of the omentum, diaphragm and liver [6].

On early stage HOC22, the lowest dosage (16.6 mg/kg) of paclitaxel and docetaxel significantly prolonged ($P < 0.001$) the survival of all mice, and induced 50 and 75% of cures, respect-

ively (Table 4). With the higher doses (20–34.5 mg/kg), all mice survived 180 days after tumour transplant without visible tumours in the peritoneal cavity. Microscopic analysis after autopsy showed that only one mouse given 20 mg/kg paclitaxel presented micrometastasis in the liver, two mice given 20 mg/kg docetaxel showed micrometastasis to the omentum, and one mouse showed micrometastasis to the diaphragm. One toxic death occurred with paclitaxel at 34.5 mg/kg on day 9.

DDP produced one toxic death after the third injection (day 15) and was active, significantly prolonging ($P < 0.05$) survival of all the mice (ILS 126%) but without any cures (Table 4).

Paclitaxel and docetaxel significantly prolonged the survival of mice with advanced stage HOC22 growing in the peritoneal cavity (Table 5), with ILS of 216% ($P < 0.001$) and 295% ($P < 0.001$), respectively, at the dose of 20 mg/kg. The higher dose (34.5 mg/kg) induced ILS of 326% ($P < 0.001$) and 444% ($P < 0.001$) (Table 5). Despite the delay in tumour growth and the significant increase in survival time, none of the mice gave a complete response with either drug. In fact, all the mice died with heavy tumour burden in the peritoneal cavity.

DDP, the reference drug, was less active than paclitaxel and docetaxel, but did prolong survival, with an ILS of 97% ($P < 0.05$) (Table 5).

DISCUSSION

This study compared the antitumour activity of two taxoids, paclitaxel and docetaxel, against HOC xenografts. In four ovarian carcinoma nude mouse models, these drugs showed similar antitumour activity and were always more active than DDP, which was used as a reference compound. Paclitaxel and docetaxel were highly active against HOC22-S and HOC18 growing s.c. in nude mice, with a high cure rate 60 days after treatment. HOC22-S was marginally more sensitive than HOC18. Equiactive doses of paclitaxel and docetaxel had similar effects against HOC22-S. On HOC18, low doses of docetaxel (16.6–20 mg/kg) seemed to achieve a higher percentage of complete tumour regressions although at equitoxic doses (9–10% body weight loss) paclitaxel appeared to induce more cures (Table 2). Therefore, no substantial differences were found in the activities of paclitaxel and docetaxel on HOC18.

Subcutaneous tumours are a convenient model for assessing tumour response to chemotherapy when the tumour size has to be measured frequently [32]. However, while s.c. xenograft tumours are commonly studied, their anatomical localisation does not reproduce the pattern of growth of human ovarian cancers [31]. Tumours transplanted s.c. in nude mice are circumscribed and often lack local invasion and distant metastases [33]. In contrast, ovarian tumour cells transplanted in the peritoneal cavity of nude mice produce ascites and intra-abdominal carcinomatosis, mimicking the growth pattern of the human disease [31, 34, 55].

Paclitaxel and docetaxel had significant activity against HOC8 and HOC22 growing in the peritoneal cavity of nude mice (Tables 3–5). As we have shown before [6], HOC22 growing in the peritoneal cavity of nude mice was more sensitive than HOC8 to paclitaxel treatment. Here we found paclitaxel and docetaxel had comparable activities on the two tumours transplanted i.p. In fact, at the highest tolerated dosage, both drugs given to mice bearing early stage tumours, induced 100% cure rates among mice transplanted with HOC22 and 60% for mice with HOC8.

In advanced stage HOC22 tumours, paclitaxel markedly prolonged the life span of the mice, but there were no cures [6]. Similarly, the same doses of docetaxel delayed growth and significantly prolonged life span. Thus, paclitaxel and docetaxel are also effective when tumour burden is high, but neither compound had any advantage over the other.

Paclitaxel and docetaxel were active on HOC22-S growing s.c. as well as on HOC22 growing i.p. in nude mice, so both models are suitable for assessing the activity of antineoplastic drugs. However, the two experimental systems give different information: the s.c. growing tumour has the advantage that the response to a drug can be followed during treatment, but the i.p. model provides additional information on whether a compound inhibits ascites formation and tumour dissemination in the peritoneal viscera.

Earlier preclinical studies with paclitaxel indicated a good spectrum of activity against a few tumour models. Most of these studies involved i.p. or s.c. therapy with suspended paclitaxel that was ineffective against most distal site tumour models [4, 5, 36]. The use of better suspending agents means that paclitaxel can now be administered better, resulting in activity against a variety of tumour models [5]. Docetaxel is a more water soluble drug, and was found to be active i.v. and i.p. against distal tumour implants [16]. Here, paclitaxel and docetaxel administered i.v. in an ethanol-based vehicle were active against s.c. and i.p. transplanted HOC, thus confirming their activity in distal site tumour models.

In the HOC models used here we found no significant differences between the two drugs. Docetaxel was found to be more toxic on a mg/kg basis than paclitaxel. However, adequate efficacy comparison could not be made as we did not always reach the maximum tolerated dose with paclitaxel, probably due to solubility limitations.

It is interesting to note that docetaxel was found to be more potent in promoting tubulin polymerisation [17, 20] and that *in vitro* cell lines were two to five times more sensitive to docetaxel than paclitaxel [19–21]. It would be interesting to see whether these differences seen *in vitro* do translate to differences *in vivo*. However, little information is available on the comparative efficacy of the two drugs *in vivo*, except for comparison against M109 murine lung carcinoma and A2780 human melanoma, where the two drugs showed similar activity [37], and B16 murine melanoma where docetaxel was more active than paclitaxel [16].

Our results on HOC xenografts constitute the first such comparison on human tumours. The present work shows that paclitaxel and docetaxel have similar antitumour activities, acting against human ovarian cancer xenografts and are better than DDP which is one of the most effective drugs against these tumours, either transplanted in nude mice [38, 39] or in patients [40].

These results provide a further basis for the investigation of these drugs in first-line chemotherapy after surgery as an alternative to or in combination with DDP. The combination would be justified by the fact that paclitaxel or docetaxel and DDP have different modes of action, with no cross-resistance [20, 41] nor overlapping toxicities [42]. The ovarian tumour xenografts used in the present study could be valuable for investigating how to combine paclitaxel or docetaxel and DDP in the most effective way. Considering their high sensitivity to both paclitaxel and docetaxel, these ovarian carcinoma xenografts could be used to elucidate the biochemical determinants of tumour susceptibility to these drugs, and to test new natural products.

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