Pergamon

European Journal of Cancer, Vol. 33, No. 13, pp. 2183–2193, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00260-8

Clinical Oncology Update

Review of Recent Trials of Chemotherapy for Advanced Breast Cancer: the Taxanes

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INTRODUCTION

THE TAXANES are a relatively new class of chemotherapeutic agents which act specifically on the microtubules of the cell spindle, resulting in disruption of mitosis, and therefore cell proliferation. There are currently two taxanes which have been clinically tested, paclitaxel (Taxol) and docetaxel (Taxotere), and both have shown antitumour activity against breast cancer in clinical trials. These are summarised in this review.

PACLITAXEL

Single agent

One of the most notable phenomena related to clinical trials in breast cancer in 1995–1996 is the explosion of studies on paclitaxel. So many studies have been performed that a systematic review detailing all of them is impossible in the space available. The vast majority of these are non-randomised, open-label studies of phase I/II type. 22 such studies have been performed using paclitaxel as a single agent and addressed toxicity, searching for the maximum tolerated dose (MTD) through dose escalation and investigating different administration schedules (Tables 1 and 2). Many of these studies also reported responses. These studies show that doses of 200 mg/m^2 are relatively well tolerated in chemotherapy-naïve patients and can be safely escalated to 250 mg/m^2 or even higher. At the higher doses, neurotoxicity becomes more severe and may be the dose-limiting toxicity [1]. Liver dysfunction has also been found to very significantly exacerbate toxicity [2]. While earlier studies used 24 h infusions, 3 h infusion times have been found to be safe as well. In patients who have received prior chemotherapy, some studies reduced the dose to 175 mg/m^2, but in those that persisted at 200 or 250 mg/m^2 toxicity was manageable [3] (Table 1). Responses including complete responses were seen in all studies. In minimally pretreated patients, the objective response rate ranged from 32 to 56%; lower response rates were seen in regimens with lower doses, suggesting a dose–response relationship. Among pretreated patients, an objective response rate of 6–47% has been reported and paclitaxel appears to retain activity even in anthracycline-resistant disease [3] and after previous paclitaxel treatment [4]. Median duration of response was reported in 11 studies and ranged from 6 to 9 months in minimally pretreated patients and 4–7 months in pretreated patients (Table 1).

In five randomised trials using paclitaxel (Table 2), three studies compared dose levels or administration schedules. These studies have shown that 175 mg/m^2 gives a very slightly better response rate (RR) to 135 mg/m^2 with a similar toxicity (RR = 29% versus 22% with approximately 220 patients in each arm) [11], and toxicity is similar comparing a 3 h infusion with a 24 h infusion [54] but less in a 96 h infusion [55]. A phase III randomised trial compared paclitaxel with mitomycin C at a dose of 12 mg/m^2 [12]. In heavily pretreated patients, responses were seen in 17% of those receiving paclitaxel compared to 6% in the control arm with 36 patients in each arm. In another phase III trial, paclitaxel was compared wth CMFP (cyclophosphamide, methotrexate, fluorouracil, prednisolone) in untreated patients [99]. Toxicity was worse in the CMFP arm, although the RR and TTP (time to progression) were better than in the pacitaxel arm. However, overall survival was better with paclitaxel.

Paclitaxel in combination

Another 45 studies have investigated paclitaxel with other drugs, principally anthracyclines (Table 3), platinum (Table 4) and alkylating agents (six studies). Other studies used combinations with 5-fluorouracil (5-FU), and a variety of multidrug combinations (Table 5). Six studies used paclitaxel in high dose regimens supported by PBSC (peripheral blood stem cell) (Table 6).

Paclitaxel 200 mg/m^2 with 60 mg/m^2 doxorubicin or 60–90 mg/m^2 epirubicin was found to be generally tolerable in previously untreated patients. However, significant cardiac toxicity was observed in approximately 20% of patients in some studies at this dose level [5–7]. Sequencing was investigated, with reports suggesting either no effect [5] or less toxicity when the anthracycline was given before paclitaxel [8, 9]. Response rates were generally higher in these studies than in the single-agent studies ranging from 44 to 100% with anthracycline combinations. Median duration of responses were also slightly better than in single-agent treatment ranging from 8 to 11 months, although only three studies reported these data.

Paclitaxel/platinum combinations (Table 4) were found to increase neurotoxicity significantly at doses of 200 mg/m^2 paclitaxel and 60–75 mg/m^2 cisplatin [10]. Response rates

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Received 22 Apr. 1997; accepted 6 May 1997.

Table 1. Single-agent paclitaxel non-randomised trials

Ref.	No. of pts entered	No. of evaluable pts	Patient selection	Dose (mg/m^2)	Infusion time (h)	G-CSF	CR	PR	RR	Response duration	Comments
[1]	36	36	Poor prognostic group of breast cancer patients who progressed or relapsed while taking anthracyclines	250–300	3	yes			6% (2 pts)	16 and 18 weeks	Neurotoxicity is DLT at this dose (83%)
[2]			Adjuvant CT only	150 every 2 weeks	3	no			no data		Toxicity is proportional to liver dysfunction
[3]	25	25	Second CT regimen for stage IV disease	250	24	no	1/25	7/25	32%	7 mo	This study confirms activity in heavily pretreated patients
	52	52	Third or subsequent CT regimen	200	24	yes			30%	7 mo	
	77	76	Both of the above	200 or 250			2/76		32%	4 mo	Combined results
[4]	26		Previous progression while receiving paclitaxel at 3 h infusion	120–140	96	no			27%	6 mo	
[8, 17]	25		1 previous CT regimen	250	24	no	12%	44%	56%	9 mo	Overall survival was 21 mo
			Heavily pretreated	150-175	24	no			20%		Moderate activity at this dose
[19]	24	24	Two or more prior regimens, including an anthracycline	175	3	no			21%	4 mo	3 h infusion is safe
[21]	29		Refractory to paclitaxel	200	3	no but verapamil 75–250 mg					No response data
[22]	36	35	Extensive pretreatment	225	3	no			34%	7 mo	
	15	15	Extensive pretreatment, progression within 12 months	175	3	no	7/50	12/50 both	47%		Sequential test of two doses, higher dose has more toxicity but no more efficacy. TTP = 5 mo
[45]	19	19	Prior adjuvant CT	135	24	no	2/19	4/19	32%	37.5 wks	
[46]	120	101	Prior adjuvant or neo-adjuvant CT	225	3	no	6/101	38/101	44%		Toxicity acceptable at this dose
[47]	119	74	1 previous CT for MBC	210	3	no	2/74	10/74	18%		3 treatment deaths. QOL improvement in 40% TTP, 4 mo; OS, 11 mo
[48]	11	11	Previous treatment either CMF or anthracycline	175	3	no	0	4/11	36%	10 wks	Limited effect in resistant disease
[49]	50	46	2nd line for MBC	225	3	no	2/46	11/46	28%		
[50]	21	21	Previous anthracycline				1/21	1/21		6 and 9 mo	Low activity in previous anthracycline failure
[51]	6		Liver metastases	175	3	no	0	3/6			
[52]		16	Previous paclitaxel	140	96	yes and verapamil	0	0	0		
[53]		82	PAT	250	3	yes	14/82	21/82	43%		

DLT, dose limiting toxicity; G-CSF, granulocyte-colony stimulating factor; CR, complete response; PR, partial response; RR, response rate; TTP, time to progression; CT, chemotherapy; OS, overall survival; MBC, metastatic breast cancer; QOL, quality of life; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; PAT, prior anthracycline treatment.

Table 2. Single-agent paclitaxel randomised trials

Ref.	No. of pts entered	No. of evaluable pts	Patient selection	Dose (mg/m^2)	Infusion time (h)	G-CSF	CR	PR	RR	TTP	Survival	Comments
[11]	471	223	Patients with metastatic breast cancer, who had failed to respond to previous chemotherapy	175	3	no	12/223	53/223	29%	4.2	11.7	Moderate efficacy and safety in previously treated pts
				versus								
		227		135	3	no	5/227	46/227	22%	3	10.5	
[12]	81	36	All patients previously received chemotherapy for metastatic disease, and half had both adjuvant therapy and chemotherapy for metastatic disease	175	3	no			17%	3.5		Active and safe
				versus								
		36		Mito C 12	intravenous bolus	no			6%	1.6		
[54]		521 (both groups)		175	3	no			29%	3.8	9.8	No significant advantage from 24 h infusion
					versus							
				175	24	no			32%	4.6	13.4	
[55]		60		250	3							Less toxicity in 96 h infusion
				versus								
		63		140	96							
[99]	208	100	Previously untreated patients	200	3	no			31%	5.5	16.5	More admissions for febrile neutropenia in CMFP arm and more mucositis
				versus								
				CMFP C 100 × 2 M 40 × 2 F 600 × 2 Pred 40 × 14		no			36%	6.4	11.3	

See legend of Table 1 for abbreviations. CMFP, Cyclophosphamide, methotrexate, 5-fluorouracil, prednisolone.

Table 3. Paclitaxel and anthracyclines first-line in metastatic breast cancer

Ref.	No. of pts entered	No. of evaluable pts	Patient selection	Dose (mg/m^2)	Infusion time (h)	Dox dose (mg/m^2)	G-CSF	CR	PR	RR	Response duration	Comments
[5]	35	32	Untreated pts with metastatic breast cancer	125–200		60	no	13/32	17/32	94%	8–11 mo	Dose finding study. 18% CHF. MTD = 200 mg/m^2, sequence alternated not found to be important
[6, 7]		32	Minimally pretreated (at most 1 previous adjuvant CT)	125–200	3	60	no	7/29	17/29	83%		20% CCF. TTP, 9 mo
[8]	10			125	24	60	yes	1/10	7/10			DOX reduced to 48 mg/m^2 MTD
	21			150	24	60						Sequence P- > D worse toxicity
[9] and [59]	19	19	11 had PAT	130–250	3	50	no	6/19	9/19	78.8%	8 + mo	Sequence is important D- > P
[24] and [60]	72	46	15 had PAT	175–225	3	60 (epi)	no	6/46	31/46	58.7%		
[25] and [61]	28	22	Prior adjuvant CT	135–225	3	90 (epi)	yes	13%	66%	83%		Dose escalation study. No cardiac toxicity. MTD not reached
[26]	42	39	30 had no CT, 12 had PAT	160–200	72	45–60	yes	3/39	25/39	72%	9 mo	TTP, 12 mo. OS, 23 mo
[27]	31	25		110–250	3	50–60 (epi)	no	0	11/25	44%		MTD P = 200 mg/m^2, EPI = 60 mg/m^2. Some cardiac toxicity
[56]	49	47		200	3	60	yes	19/47	25/47	94%		G-CSF had no effect on clinical episodes of febrile neutropenia or infection. TTP, 13 mo OS, 85% at 16 mo
[58]	25	25	19 had PAT	250	2–3	60	yes	7/25	13/25	80%		
[63]	24		No previous CT	135	3	75	yes					No response data. Cycle shortening
[64]	26	23	12 had PAT, 12 were previously treated Previous MTX 12 (Significant pre-treatment)	175	3	10–14 (mitox)	no	4/23	11/23	65%		4.3% cardiac toxicity
[65]	17	7	PAT	175	3	60–90		7/7		100%		Sequential administration

CHF, congestive heart failure; MTD, maximum tolerated dose; MTX, methotrexate; PAT, prior anthracycline treatment; DOX, doxorubicin; PT, previously treated; P- > D, paclitaxel followed by doxorubicin; D- > P, doxorubicin followed by paclitaxel; epi, epirubicin; mitox, mitoxantrone; MTD, maximum tolerated dose; CT, chemotherapy.

Table 4. Paclitaxel and platinum

Ref.	No. of pts entered	No. of evaluable pts	Patient selection	Dose (mg/m^2)	Infusion time (h)	Cisplatin dose	G-CSF	CR	PR	RR	Response duration	TTP	Survival	Comments
[10]	44	41	19 had no previous CT or PAT, 22 had neoadjuvant CT	200	24	75	yes	5/42	17/42	53%		8.6 mo		Significant neurotoxicity and 1 toxic death
[28–30]	29	27	All but two of the women had received prior adjuvant CT	90 every 2 weeks	3	60	no	3/27	18/27	85% (78%)	7.9 mo	7.1 mo		Safe and active
[66]	17	17	PAT with anthracycline	135	24	75	no	7/17	8/17	89%				
[67]	14	13	PAT	135	24	75	no	2/13	5/13	54%				
[68]	16	14		90 every 2 weeks	3	60	no	0	3/14	21%				Protocol abandoned due to low response rate. Also significant neurotoxicity
[69]	25	25	16 had PAT	90 every 2 weeks	3	60	no	3/25	12/25	60%	8 mo		11 mo	Significant neurotoxicity
[70]	39	34	PAT	200	24	75	yes	4/34	11/34	44%				Neurotoxicity is DLT
[71]	32		Anthracycline resistant	200	3	Carboplatin 7 AUC	yes	2/32	6/32	25%				

See Table 1 and Table 3 legends for abbreviations. AUC, area under the curve.

Table 5. Multidrug combinations with paclitaxel

Ref.	No. of pts entered	No. of evaluable pts	Patient selection	Dose (mg/m^2)	Infusion time (h)	Other drug dose (mg/m^2)	G-CSF	CR	PR	RR	Response duration	TTP	Survival	Comments
[31,32]	40	54	At least 1	175	3	2 g 5-FU	no	—	—	59%	9 mo	10 mo	19 mo	Safe and effective
and [72]	46 51	35	previous CT	135–175		1.5–2 g 5-FU		1/35	18/35	55%	8 mo			
[33]	38	34	previously treated	175	3	350 5-FU (d1–3)	no	—	—	62%				
		16	previously treated					2/16	9/16	69%				
[34,35]	35	34	Max 1 previous	135–250	24	750–2000 Cyclo	yes	—	—	29%				Dose escalation study
	37	36	CT for MBC					2/36	8/36	28%				
[36,37]	55	42	2 previous CT	135–160	72	Cyclo 1600 (600–3300)	yes	1/42	22/42	54%		6.2 mo		Dose escalation. MTD P = 160 mg/m^2 Cyclo = 2700 mgm^2
		44												
[38]	46	45	First or second line CT	135	1	5-FU 350 d1–3 Mitox 10 LV 300	no	2/45	21/45	51%	7.5		9.5 mo 45% 1 yr surv	3 toxic deaths (2 cardiac) Myelosuppression was more severe than expected
[73]	12	10	Previous anthracycline CT	175	3	5-FU 350–500 (d1–3) LV 100	no	0	4/10	40%	4 + mo		10 + mo	
[74]	43		Max 1 previous CT for MBC	175–200	3	750–1750 Cyclo	yes	0	3/43					
[75]	14	14	Previous adjuvant CT	170	3	1200 ifos	yes	0	4/14	28%		5 mo		
[76]		22		175	3	1800 ifos (d2–4)	no	2/22	9/22	50%	7 mo		12 mo	
[77]	18	12	previously treated	175	3	180–300 Edatrexate	no	3/12	5/12	66%				Dose escalation MTD not reached
[78]	21	18	First-line CT	150–200		Epi 50 Cyclo 500								MTD not reached
[79]	54	34	1 or more previous CT	175	3	LV 300 5-FU 350 (d1–3)	no	3/34	18/34	62%			15 + mo	
[80]	26	25	Previously heavily treated	120	3	Vinorelbine 20 Cisplat 70	yes	0	14/25	54%	6 + mo		7 + mo	
[81]		9	PAT	135–200		Cisplat 80 ifos 1500–1800	yes	1/9	5/9	6/9				

5-FU, 5-fluorouracil; Cyclo, cyclophosphamide; Mitox, mitoxantrone; LV, leucovorin; ifos, ifosfamide; Epi, epirubicin; Cisplat, cisplatin; d1–3, day 1 to 3; PT, previously treated; MBC, metastatic breast cancer; MTD, maximum tolerated dose; d2–4, day 2 to 4.

Table 6. High-dose chemotherapy for metastatic disease with paclitaxel

Ref.	No. pts entered	No. of evaluable pts	Patient selection	Dose (mg/m^2)	Infusion time (h)	Other drug dose (mg/m^2)	G-CSF	CR	PR	RR	TTP
[39]	32	26		135–625	24	Cisplat 55 (D? Cyclo 1875 d2-4	PBSC			78%	Med prog free int 3.5 mo
[82]		6	previously treated	10–25 daily × 5		Cyclo 2.5 g daily × 3 Thiotepa 225 daily × 3	yes with PBSC				1 response at 55 wk
[83]	42	33		775?	24	Cyclo 1875 D1-3 Cisplat 55 D1-3	PBSC			54%	Dose escalation 2 treatment deaths MTD not reached
[84]	22	19	previously treated	200		Cisplat 55 D4-6 Cyclo 1875 d4-6	yes with PBSC	7/19	6/19	68%	
[85]	24	24		250–400		CTX 6 g MTX 70	yes PBSC	9/24	14/24		
[86]	21			175–300		Cyclo 3 g × 2 Carbo 450 mg/m^2 × 4	yes with PBSC	10/17	3/17		DLT not reached but 2 toxic deaths

PBSC, peripheral blood stem cell; DLT, dose-limiting toxicity.

were somewhat lower than with anthracyclines ranging from 21 to 89% and one study was aborted prematurely because of perceived unacceptably low response rate. Alkylating agents have also been successfully combined with paclitaxel. Most of these studies recruited previously treated patients and doses of 175 mg/m^2 paclitaxel with up to 2.7 g/m^2 cyclophosphamide or 1.8 g/m^2 ifosfamide were used, sometimes with G-CSF (granulocyte colony stimulating factor) support. Response rates in these previously treated patients ranged from 28 to 66% with a median duration of responses of 4–9 months. Multidrug combinations (Table 5) with epirubicin and cyclophosphamide; 5-FU (with leucovorin) and mitoxantrone; or cisplatin with ifosfamide or vinorelbine have been safely given and show similar response rates. In high-dose regimens (Table 6), paclitaxel has been used both for induction/mobilisation and in the intensification phase (somewhat surprisingly in view of reports mentioned above which suggested that neurotoxicity was the dose-limiting toxicity (DLT)). These procedures have been associated with toxic deaths and response rates ranged from 54 to 78%, which are perhaps lower than expected.

Two studies evaluated paclitaxel in the adjuvant setting and three as neoadjuvant treatment (Table 7). In the adjuvant studies [40, 88, 90], follow-up is still too short to provide any meaningful data and further reports are awaited. In one neoadjuvant study [89], all patients responded with 4 of 7 CR (complete response) and 3 PR (partial response). However, in a larger study [87] with 23 patients, the objective response rate was only 35%. Nevertheless, pathological CR was confirmed in 13% of cases. One randomised trial of neoadjuvant chemotherapy compared two regimens of induction chemotherapy followed by high-dose chemotherapy with PBSC with or without paclitaxel in the induction arm [91]. 11 of 21 patients had a pathological CR in the paclitaxel treated arm (52%) compared with 4 of 23 in the control arm (17%).

Table 7. Adjuvant and neoadjuvant

Ref.	No. of pts entered	No. of evaluable pts	Patient selection	Dose (mg/m^2)	Infusion time (h)	Other drug dose (mg/m^2)	G-CSF	CR	PR	RR	Comments
[40] and [88]	42	42	Adjuvant	250 q2/52 × 3	24	Dox 90 q 2 wks × 3 Cyclo 3 g q2/52 × 3NB sequential	yes				Sequential treatment D -> P -> C versus D -> P + C D-P + C is more toxic
[87]	23	23	Neoadjuvant	200	3	Dox 60	yes	5/23	3/23	35%	pCR 13%
[89]	17	7	Neoadjuvant	140	96	Dox 60 Cyclo 200 q2/52 × 3	yes	4/7	3/7	100%	
[90]	11		Adjuvant	200–300	6	Cyclo 3 g × 2 Carbo 450 × 4	yes with PBSC				
[91]	21		Neoadjuvant	200 in induction and mobilisation		AFM induction Cyclo 3 g mobilisation	HD with Cyclo, thiotepa, carbo and PBSC	11/21 (pCR)			

q2/52, every two weeks; AFM, doxorubicin, 5-FU, methotrexate; HD, high-dose; D, doxorubicin; P, paclitaxel; C, cyclophosphamide.

Table 8. Single-agent docetaxel non-randomised trials

Ref.	No. of pts entered	No. of evaluable pts	Patient selection	Dose (mg/m²)	Infusion time (h)	G-CSF	CR	PR	RR	Response duration	TTP	Survival	Comments
[13]	35	31	Advanced breast cancer	100 q3/52	1	no	5/31	16/31	67.7%	44 + wks	37 + wks	16 + mo	No steroid medication given. Fluid retention syndrome in 26/34 pts
[14]	42	35	1 or 2 previous CT, including anthracycline. PD on treatment	100 q3/52	1	no	3/35	17/35	57%	28 wks			Grade IV neutropenia in 95% of patients Dexamethasone delayed onset of fluid retention syndrome
[15]	37	37	Previous adjuvant CT only	100 q3/52	1	no	2/37	18/37	54%	26 wks			AUC did not predict toxicity but liver failure led to raised AUC and toxic death
[16]	35	34	Strictly defined anthracycline resistant MBC	100 q3/52	1	no	0	18/34	53%	7.5 mo		9 mo	Highest response rate in visceral dominant involvement
[41]	81	72	Advanced or recurrent	60 q3/52-4/52		no	5/72	27/72	44.4%				32% RR in previous anthracycline chemo DLT = neutropenia grade 3–4 in 85.9%
[42]	37	37	Advanced breast cancer	100 q3/52	1	no	2/37	23/37	67.7%		31 wks		Steroid medication restricted to 1 day is less effective than 5 days
[43]	51	47	Previous adjuvant chemo only	75 or 100 q3/52		no	4/47	22/47	55%				Possible dose response relationship
[44]	162	129	Second-line MBC (134 pts anthracycline resistant)	100 q3/52	1	no			50%	6 mo			Highly effective even in anthracycline resistant and poor prognosis patients
[92]	94	57	MBC 1 previous chemo including adjuvant	100 q3/52	1	no	3/94	29/94	34%				
[93]	36	26	Primary or secondary paclitaxel resistant MBC	100 q3/52	1	no	1/26	2/26	11.5%				Limited anti-tumour activity in paclitaxel resistant MBC
[94]	32	28	Previously treated MBC	100 q3/52	1	no	1/28	11/28	43%				
[95]	241	217	Anthracycline resistant MBC	100 q3/52	1	no		40/217	19%	6 mo	3 mo		

q3/52, every 3 weeks. PD, Progressive disease; CT, chemotherapy; MBC, metastatic breast cancer; AUC, area under the curve; DLT, dose-limiting toxicity.

Table 9. Docetaxel in combination with other drugs

Ref.	No. of pts entered	No. of evaluable pts	Patient selection	Dose (mg/m^2)	Infusion time (h)	Other drug dose	G-CSF	CR	PR	RR	Comments
[96]	10	5	No previous CT for advanced breast cancer and no anthracycline in adjuvant CT	100	1 alternating regimen	Epirubicin: 120 mg/m^2 Cyclophosphamide: 830 mg/m^2	yes	0	5/5	100%	
[97]	15		MBC	40–60	1–2	Cyclophosphamide: 200–400 mg/m^2	no				DLT was grade IV neutopenia in 3/3 patients at top dose level
[98]	40	28	Prior adjuvant CT only	50–60	1	Doxorubicin: 40–60 mg/m^2			15/20	75%	MTD not reached

CT, chemotherapy; MBC, metastatic breast cancer; MTD, maximum tolerated dose.

DOCETAXEL

Docetaxel is also under intensive investigation. 12 studies have evaluated the drug as single-agent treatment for metastatic or advanced breast cancer (Table 8). The majority of these used 100 mg/m^2 and found this to be the MTD, with DLT grade III–IV neutropenia. Hypersensitivity reactions and fluid retention syndrome are also characteristic of this drug [13]. As for paclitaxel, the former can be largely abolished by appropriate premedication with steroids. Prolonged steroid medication (for 4 days after treatment) delays but does not prevent fluid retention syndrome [14]. Toxicity did not appear to be directly related to the AUC (area under the curve) in one study that performed detailed pharmacokinetic measurements, but in patients with significant liver dysfunction toxicity is markedly increased (and is associated with an increased AUC) [15]. Responses were reported in 54–67% of cases in patients with minimal pretreatment and in 19–57% of pretreated patients including strictly defined anthracycline-resistant tumours. In paclitaxel-resistant disease, 11% of 26 patients responded [93]. Interestingly, high response rates were reported in patients with multiple sites of disease and with visceral metastases [16].

Only three studies have reported using docetaxel in combination with other drugs (Table 9). In a dose-escalating study of docetaxel (50–60 mg/m^2) and doxorubicin (40–60 mg/m^2), the MTD had not yet been reached and 15 of 20 evaluable patients had responded [75%; ref 98].

No randomised controlled trials of docetaxel have been reported in 1995–1996.

CONCLUSION

Both paclitaxel and docetaxel appear to be highly effective in producing responses in metastatic breast cancer. If these drugs are interesting as single agents they are even more impressive when combined with other agents, particularly anthracyclines. However, responses appear to be temporary as has been found with other cytotoxic agents. Despite these exciting results there is a disappointing lack of well-conducted randomised phase III trials to confirm and measure their true contribution.

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