PERGAMON

European Journal of Cancer 38 (2002) 1992–1997

European Journal of Cancer

www.ejconline.com

Phase I study of weekly paclitaxel and liposomal doxorubicin in patients with advanced solid tumours

N. Androulakis*, C. Kouroussis, D. Mavroudis, S. Kakolyris, J. Souglakos, S. Agelaki, K. Kalbakis, K. Malas, A. Pallis, G. Samonis, V. Georgoulias

Department of Medical Oncology, University General Hospital of Heraklion, PO Box 1352, 71110 Heraklion, Crete, Greece

Received 25 October 2001; received in revised form 28 February 2002; accepted 29 May 2002

Abstract

The aim of this study was to determine the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLT) of a weekly administration of paclitaxel and pegylated liposomal doxorubicin (Caelyx; Schering Plough Pharmaceutical) in patients with advanced solid tumours. 19 pretreated patients with solid tumours received escalated doses of pegylated liposomal doxorubicin (6–12 mg/m^2) as a 1-h intravenous (i.v.) infusion followed by a fixed dose of paclitaxel (80 mg/m^2) weekly for 4 consecutive weeks in cycles of 6 weeks. DLT was defined as grade 4 neutropenia or thrombocytopenia, febrile neutropenia, grades 3 or 4 non-haematological toxicity or treatment delay due to unresolved toxicity during cycle 1. The MTD was reached at the dose of pegylated liposomal doxorubicin of 10 mg/m^2/week and paclitaxel of 80 mg/m^2/week. The DLTs were treatment delay due to grade 3 neutropenia and grade 3 diarrhoea. A total of 55 chemotherapy cycles were administered, and grades 3–4 neutropenia occurred in seven cycles (13%); the non-haematological toxicity was mild with grades 2/3 diarrhoea occurring in 4 (7%), grades 2–4 asthenia in 11 (20%) and grade 2 mucositis in 7 (13%) cycles. There was no case with more than a 10% LVEF decrease after a median of 3 (range 2–6) administered cycles/patients. One patient with breast cancer and 1 with ovarian cancer experienced a major partial response. The weekly administration of pegylated liposomal doxorubicin at the dose of 10 mg/m^2 in combination with paclitaxel at the dose of 80 mg/m^2 for 4 consecutive weeks, in cycles of 6 weeks which represent the recommended doses for further phase II studies, is a well tolerated regimen, which merits further evaluation in tumours known to be sensitive to taxanes and/or anthracyclines.

Keywords: Paclitaxel; Pegylated liposomal doxorubicin; Phase I study; Weekly chemotherapy; Solid tumors

1. Introduction

Paclitaxel (Taxol) is a chemotherapeutic agent with activity against various types of tumours. Its optimal dose and administration schedule has not yet been established. Recently, a number of trials have evaluated the dose-dense weekly administration of paclitaxel as a strategy to improve its therapeutic index and treatment options [1–4]. The rationale for this approach is that more frequent administration of moderate doses of the drug may achieve greater efficacy than higher doses every 3 weeks, through a more sustained exposure of dividing tumour cells to cytotoxic drug levels. As a consequence, patients should benefit from both a greater dose intensity and higher cumulative doses, while the lower individual doses could be less toxic.

Chemotherapy regimens combining paclitaxel with doxorubicin have shown high antitumour activity in breast cancer; however, these combinations have been complicated by severe haematological and cardiac toxicity. Indeed, up to 50% of patients receiving the paclitaxel/doxorubicin combination developed a reduction of the left ventricular ejection fraction (LVEF) below the normal level and 20% of them developed congestive heart failure [5,6].

In an effort to reduce toxicity, while maintaining the same level of activity, doxorubicin has been entrapped in liposomes. Doxorubicin hydrochloride pegylated liposomes, known as 'Caelyx' in Europe and 'Doxil' in the US, is a liposomal formulation of doxorubicin, sterically stabilised by the grafting of segments of polyethylene glycol onto the liposomal surface. This new

* Corresponding author. Tel.: +30-810-392747; fax: +30-810-392802.

E-mail address: georgsec@med.uoc.gr (N. Androulakis).

0959-8049/02/$ - see front matter
PII: S0959-8049(02)00168-5

type of liposome avoids the rapid hepatic uptake and has been documented to circulate for prolonged periods in the bloodstream and to accumulate in tissues with increased vascular permeability, such as tumour tissues, whereas its concentration in the cardiac muscle remains low [7–10]. In animal tumour models, pegylated liposomal doxorubicin has shown superior activity and reduced toxicity compared with free doxorubicin [11–13]. Clinical trials have shown that pegylated liposomal doxorubicin is active against various types of tumours with palmar-plantar erythrodysesthesia (PPE) and mucositis being the two main dose-limiting toxicities (DLT); conversely, myelosuppression, nausea, alopecia and cardiotoxicity are less common and less severe compared with free doxorubicin [14–18]. In these trials, different doses and administration schedules have been used and recently the feasibility of the weekly administration of pegylated liposomal doxorubicin has been reported [19].

Although there is considerable experience with the combination of doxorubicin and taxanes, the data regarding the weekly use of liposomal pegylated anthracyclines and taxanes are preliminary [20–25]. Therefore, we conducted a phase I trial to determine the maximum tolerated doses (MTDs) and the DLT of the paclitaxel/pegylated liposomal doxorubicin combination administered weekly. This administration schedule was chosen in order to reduce the dose and sequence-dependent toxicities based on the experience of the combination of paclitaxel with either conventional or liposomal doxorubicin [26–29].

2. Patients and methods

2.1. Patient selection

Patients with histologically- or cytologically-confirmed advanced stage solid tumours who had disease progression after one or two chemotherapy regimens were enrolled onto the study. Prior radiotherapy (to less than 20% of bone marrow-containing bones) or chemotherapy were allowed, but a treatment-free interval of at least 4 weeks was required before entering the study. Other inclusion criteria were: age 18–75 years, performance status World Health Organization (WHO) 0-2, life expectancy of at least 3 months, adequate blood counts (absolute neutrophil count $\geqslant 1500\times10^6$ cells/l, platelets $\geqslant 100\ 000\times10^6$ cells/l), renal (serum creatinine $\leqslant 132.6$ mg/dl), liver aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), alkaline phospatase, bilirubin $\leqslant 2$ times upper normal limit) and cardiac function, absence of active infection or severe malnutrition (loss of more than 20% of the body weight) and absence of any psychological or geographical condition potentially hampering compliance with the study protocol. Patients who had received prior doxorubicin-based chemotherapy had to have a LVEF $> 50\%$ evaluated by multigated (MUGA) scan. The presence of measurable disease was not required. All patients were required to provide written informed consent before entering the study. The study was approved by the Ethics and Scientific Committees of our Institute.

2.2. Treatment plan

Escalating doses of pegylated liposomal doxorubicin (pegylated liposomal doxorubicin; Schering Plough Pharmaceutical, Kenilworth, NJ, USA) were administered on days 1, 8, 15, 22 as a 1-h infusion followed by a fixed (80 mg/m^2/week) dose of paclitaxel (Taxol; Bristol Myers Squibb Co, Princeton, NJ, USA) on the same days as a 1-h infusion in cycles of 6 weeks. The starting dose for the pegylated liposomal doxorubicin was 6 mg/m^2 and it was escalated in increments of 2 mg/m^2 for each dose level. Premedication and prophylactic antiemetic regimens included 16 mg of dexamethasone, 300 mg of ranitidine and 8 mg of ondansetron given as a short intravenous (i.v.) infusion before the administration of pegylated liposomal doxorubicin. The treatment was administered on scheduled days if the absolute neutrophil count was $\geqslant 1000\times10^6$ cells/l, platelets $\geqslant 75\ 000\times10^6$ cells/l and all other toxicities resolved to grade $\leqslant 1$. Otherwise treatment was postponed until the resolution of all toxicities and was then repeated with the dose defined by the previous dose level. Patients requiring more than 2 weeks treatment delay for any reason or experiencing a decrease of the LVEF $> 15\%$ below the baseline values with or without clinical signs of congestive heart failure (CHF) were taken off the study. Patients who developed DLTs at any cycle of the treatment, received the same treatment as dosed at the previous dose level. Patients continued treatment until administration of the maximum cumulative doxorubicin dose (500–550 mg/m^2, including prior doxorubicin or 4-epiadriamycin), prohibitive toxicity, progressive disease or achievement of maximal response. Patients with responding disease were permitted to continue on paclitaxel alone.

2.3. Dose escalation

The following dose levels (mg/m^2) for the Pegylated liposomal doxorubicin/paclitaxel combination have been evaluated: 6/80, 8/80, 10/80, 12/80. No intrapatient dose escalation was allowed. At least 3 patients were enrolled at each dose level. If 1 of them experienced a DLT, 3 additional patients were treated with the same doses. If at least 50% of the patients in a certain dose level experienced DLT, the study was completed and the MTD dose level, which is recommended for further phase II studies, was the previous level below the DLT

dose level. The DLT was assessed during the first chemotherapy cycle and was defined as the occurrence of any of the following: grade 4 neutropenia or thrombocytopenia lasting for more than 5 days; febrile neutropenia; any non-haematological toxicity of grade $\geqslant 3$; any delay of treatment for more than 2 days due to unresolved haematological or non-haematological toxicity.

2.4. Patients' evaluation

Baseline evaluation should be completed within 14 days of registration and included clinical examination, full blood count with differential and platelets count, serum chemistry, electrocardiogram (ECG), chest X-rays, thorax and abdomen computerised tomography (CT) scans, bone scintigraphy and MUGA scan. Clinical examination, full blood count with differential and platelets count and serum chemistry were performed weekly. MUGA scan was performed every two cycles. Disease was assessed every two cycles by the same methods used in the baseline evaluation. Toxicities were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria [30] and evaluation of response was performed according to the WHO Criteria [31]. All patients receiving at least one cycle of treatment were evaluable for toxicity and patients with bi-dimensionally measurable disease receiving at least two cycles were evaluable for response. After treatment, patients were followed monthly until disease progression every 4 weeks by clinical examination, full blood test, serum chemistry and any other test that the responsible physician considered necessary.

3. Results

From October 1999 to February 2001, 19 patients were enrolled onto the study. All patients were evaluable for toxicity. Median age was 55 years (33–74 years), the performance status was 0–1 in 68%, and nine (47%) patients had received two chemotherapy regimens; 13 (68%) patients had $\geqslant 2$ involved disease sites. 11 patients had previously received a taxane-containing regimen and 5 of them an anthracycline one. For patients receiving the study regimen as second-line therapy, the median interval from the end of the prior chemotherapy was 3 months (range 1–10 months), while for those receiving it as third-line therapy, the corresponding interval was 1 month (range 1–3 months). 3 patients had received prior radiotherapy. For all patients, the median treatment-free interval before entering the study was 6 weeks (range: 4–40 weeks). Patients' characteristics are shown in Table 1. As there was an initial doubt about the characterisation of a toxicity at the dose level 2, 1 additional patient was enrolled at that level.

Table 1
Patients' characteristics

	No. of patients	(%)
Patients enrolled	19	
Evaluable for toxicity	19	
Evaluable for response	12	
Age		
Median (range)	55 (33–74)	
Gender		
Male/female	7/12	
Performance status (WHO)		
0	8	(42)
1	5	(26)
2	6	(32)
Previous chemotherapy regimens		
1	10	(53)
2	9	(47)
Previous anthracycline CT	5	(26)
Previous taxane CT	11	(58)
Type of tumour		
Breast cancer	5	
Ovarian cancer	3	
Gastric cancer	2	
Cancer of unknown primary	2	
Head and neck tumours	2	
Other	5	

WHO, World Health Organization; CT, chemotherapy.

3.1. Dose-limiting toxicities

Table 2 shows the dose escalation levels, the number of patients enrolled at each dose level and the observed DLT occurring during the first cycle. Grade 3 neutropenia resulting in treatment delay was the DLT in all but 1 patient where grade 3 diarrhoea was the DLT. At the fourth dose level, 3 out of 6 patients developed DLTs (in all cases treatment delay due to grade 3 neutropenia) and therefore this was considered as the DLT level. The MTDs, which correspond to the doses recommended for future phase II studies, were pegylated liposomal doxorubicin 10 mg/m^2 and paclitaxel 80 mg/m^2 administered weekly for 4 consecutive weeks in cycles of 6 weeks.

3.2. Haematological and non-haematological toxicities

Fifty-five chemotherapy cycles were administered with a median of three cycles/patient (range 2–6 cycles). The median interval between cycles was 36 days (range 36–42 days). Table 3 shows the number of patients and the number of cycles complicated with grades 2–4 toxicities during all cycles and by dose level. Six (11%) and one (2%) cycles were complicated by grades 3 and 4 neutropenia, respectively. No more than grade 2 anaemia or grade 1 thrombocytopenia were observed. Non-haematological toxicity included grade 2 nausea/vomiting in 9%, grades 2–3 diarrhoea in 7%, grades 2–4

Table 2
Dose escalation levels, number of patients enrolled and DLTs during the first cycle

Dose level	Pegylated liposomal doxorubicin (mg/m^2)	Paclitaxel (mg/m^2)	No. of patients	DLT (no. of patients)
1	6	80	3	–
2	8	80	4	–
3	10	80	6	Treatment delay (grade 3 neutropenia (1); grade 3 diarrhoea (1))
4	12	80	6	Treatment delay (grade 3 neutropenia (3))

DLT, dose-limiting toxicity.

Table 3
Worst grades 2–4 toxicities per patient during all cycles

Dose level	No. of patients	Neutropenia grade			Anaemia grade			Thrombocytopenia grade			Nausea/vomiting grade			Diarrhoea grade			Mucositis grade			Asthenia grade		
		2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
1	3 (12)	3[a] (7)	–	–	1 (2)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1 (2)	–	–
2	4 (9)	– (1)	1 (1)	–	1 (1)	–	–	–	–	–	2 (4)	–	–	1 (1)	–	–	1 (1)	–	–	1 (1)	–	1 (2)
3	6 (18)	2 (7)	1 (1)	–	–	–	–	–	–	–	1 (1)	–	–	–	1 (1)	–	1 (2)	–	–	2 (2)	1 (1)	–
4	6 (16)	2 (2)	3 (4)	1 (1)	2 (3)	–	–	–	–	–	–	–	–	1 (2)	–	–	2 (4)	–	–	2 (2)	1 (1)	–

In parentheses is indicated the number of chemotherapy cycles complicated with grades 2–4 toxicities.
[a] Number of patients.

asthenia in 20% and grade 2 mucositis in 13% of the cycles. Other non-haematological toxicities including PPE were mild and did not exceed grade 1. No patient developed congestive heart failure or reduction in the LVEF of more than 10% of the baseline values, whilst 15 patients experienced grade 2 alopecia. Two patients developed hypersensitivity reactions (flushing, headache, chills, shortness of breath) during the first administration of pegylated liposomal doxorubicin. The symptoms were resolved after discontinuation of pegylated liposomal doxorubicin and patients were successfully retreated with pegylated liposomal doxorubicin using a slower infusion rate. Due to the toxicities observed, six (11%) of the treatment cycles were delayed and another six (11%) cycles were given at a reduced dose from that initially assigned.

Table 4 shows the protocol scheduled and the administered median and relative dose for paclitaxel and pegylated liposomal doxorubicin at the different dose levels. The median cumulative administered dose was 36 mg/m^2 (range 18–48 mg/m^2) for pegylated liposomal doxorubicin and 293 mg/m^2 (range 200–340 mg/m^2) for paclitaxel.

3.3. Response to treatment

16 patients with bi-dimensionally measurable disease were evaluable for response. 2 patients had a partial response and 3 stable disease. The partial responses were documented in a patient with ovarian cancer resistant to paclitaxel–cisplatin chemotherapy and in a patient with breast cancer receiving second-line treatment

Table 4
The protocol-planned and the administered median (with range) and relative dose intensity for paclitaxel and pegylated liposomal doxorubicin at the different dose levels

Dose level	Dose intensity					
	Paclitaxel			Pegylated liposomal doxorubicin		
	Planned mg/m^2/week	Median administered mg/m^2/week	Relative %	Planned mg/m^2/week	Median administered mg/m^2/week	Relative %
1	64	55 (44–56)	86 (69–87.5)	4.8	4.2 (3.3–4.5)	88 (37–39)
2	64	51 (40–64)	80 (62.5–100)	6.4	5.1 (4–6.4)	80 (62.5–100)
3	64	62.5 (54–64)	97.5 (84–100)	8	7.6 (6.6–8)	95 (83–100)
4	64	48 (33–64)	75 (52–100)	9.6	7.2 (5–9.6)	75 (52–100)

Dose intensity is expressed as mg/m^2/week. Relative dose intensity is expressed as the percentage of the protocol planned dose.

after disease progression on an anthracycline-based regimen. The duration of the responses were 6 and 2.5 months, respectively.

4. Discussion

The goal of attenuating drug toxicities through liposomal encapsulation has been pursued for nearly two decades [32,33]. Caelyx, a liposomal pegylated formulation of doxorubicin, sterically stabilised by the grafting of segments of polyethylene glycol onto the liposomal surface, has been shown to reduce nausea, vomiting, alopecia and the propensity of cumulative cardiomyopathy [15,17,18]. As a result of its long half-life (from 45 to 70 h), skin and mucosal toxicities are the most prevalent and nearly the only toxic events experienced [8,34]. The toxicity of pegylated doxorubicin is dose- and schedule-related with stomatitis being more frequent and severe at higher doses, while shorter dosing intervals lead to an increased incidence and severity of skin manifestations [35–37]. Based on the improved acute toxicity profile and the clinical activity observed in resistant tumours, pegylated liposomal doxorubicin is considered to be a suitable drug for combination regimens.

The interest for weekly administrated regimens has been renewed since they might improve the therapeutic index; however, the paucity of data in the literature regarding the combination of taxanes with liposomal pegylated doxorubicin enabled us to combine pegylated liposomal doxorubicin with paclitaxel in a weekly administration schedule in order to determine the MTD and the DLT of the combination. The administration schedule and the sequence was based on the previous experience from combinations of paclitaxel with both pegylated liposomal doxorubicin and doxorubicin [5,6,20–27]. To the best of our knowledge, this is the first trial where both pegylated liposomal doxorubicin and paclitaxel were combined on a weekly basis. The patients of our study had a poor prognosis since all of them had progressed after front-line chemotherapy and had extensive metastatic disease. Grade 3 neutropenia resulting in treatment delay and grade 3 diarrhoea were the dose-limiting events. Severe grade 4 neutropenia was uncommon and there was no episode of febrile neutropenia. Grades 2–4 asthenia was the most common non-haematological cumulative toxicity resulting in the discontinuation of treatment in one case. However, since the majority of the patients experienced progressive disease, it is not clear whether asthenia is attributable exclusively to the chemotherapy regimen. Mucositis and PPE, the two main toxicities of pegylated liposomal doxorubicin, were uncommon probably due to the low cumulative doses administered [32]. Cardiac toxicities, in terms of CHF or reduction of the LVEF, were not observed. According to the results of our study the recommended doses for future phase II studies are pegylated liposomal doxorubicin 10 mg/m^2 and paclitaxel 80 mg/m^2 on the same day for 4 consecutive weeks in cycles of 6 weeks.

Similar results in terms of feasibility and toxicity have been reported from other studies following different administration schedules of this particular combination [20–23] including those where paclitaxel was administered weekly [20,23]. Meanwhile, some preliminary data concerning the combination of pegylated liposomal doxorubicin with the other taxane, docetaxel, have been reported [24,25]. The results were quite similar, with the exception of a higher incidence of hypersensitivity reactions observed in one study [25].

Given the increased interest for weekly schedules and the expanding list of tumours where pegylated liposomal doxorubicin and paclitaxel have been proven to be active, this combination merits further evaluation in phase II studies. In addition, it would be of interest to investigate the cardiac toxicity of the paclitaxel–caelyx—trastuzumab (Herceptin) in patients with HER2/c-neu-overexpressing breast and ovarian cancer, since the absence of cardiac toxicity of the weekly paclitaxel–caelyx might not totally exclude toxicity of this regimen in combination with trastuzumab.

Acknowledgements

This work was partly supported by the Cretan Association for Biomedical Research (CABR).

References

1. Klaassen U, Wilke H, Strumberg D, Eberhardt W, Korn M, Seeber S. Phase I study with weekly 1 h infusion of paclitaxel in heavily pretreated patients with metastatic breast cancer. *Eur J Cancer* 1996, **32A**, 547–549.
2. Akerly W, Glantz M, Choy H, *et al*. Phase I trial of weekly paclitaxel in advanced lung cancer. *J Clin Oncol* 1998, **16**, 153–158.
3. Breier S, Lebendinsky C, Ayaviri C, *et al*. Long term weekly paclitaxel over 1 hour infusion with de-escalated premedication: a phase II trial report. *Breast Cancer Res Treat* 1999, **57**, 124.
4. Markman M, Baker M, Hall JB, Spitz DL. Phase II trial of weekly single agent paclitaxel (P) in platinum (PLAT) and paclitaxel refractory ovarian cancer (OC). *Proc Am Soc Clin Oncol* 2000, **19**, 396a.
5. Dombernowsky P, Gehl J, Boesgaard M, Paaske T, Jensen BV. Doxorubicin and paclitaxel, a highly active combination in the treatment of metastatic breast cancer. *Semin Oncol* 1996, **23**(Suppl. 11), 23–27.
6. Gianni L, Munzone E, Carpi G, *et al*. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumour efficacy and cardiac effects in a dose finding and sequence finding study. *J Clin Oncol* 1995, **13**, 2688–2699.

7. De Valeriola D, Awada A, Roy J-A, Di Leo A, Biganzoli L, Piccart M. Breast cancer therapies in development. A review of their pharmacology and clinical potention. *Drugs* 1997, **54**, 385–413.
8. Working PK, Newman MS, Huang SK, Mayhew E, Vaage J, Lasic DD. Pharmacokinetics, biodistribution and therapeutic efficacy of doxorubicin encapsulated in stealth liposomes (Doxil). *J Liposom Res* 1994, **4**, 667–687.
9. Woodle MC, Lasic DD. Sterically stabilized liposomes. *Biochim Biophys Acta* 1992, **1113**, 171–199.
10. Stewart S, Harrington KJ. The biodistribution and pharmacokinetics of stealth liposomes in patients with solid tumors. *Oncology* 1997, **10**, 33–37.
11. Papahadjopoulos D, Allen TM, Gabizon A, *et al*. Sterically stabilized liposomes: improvements in pharmacokinetics and antitumor therapeutic efficacy. *Proc Natl Acad Sci USA* 1991, **88**, 11460–11464.
12. Vaage J, Mayhew E, Lasic DD, Martin FJ. Therapy of primary and metastatic mouse mammary carcinoma with doxorubicin encapsulated in long circulating liposomes. *Int J Cancer* 1992, **51**, 942–948.
13. Cabanes A, Tsemach D, Goren D, Horowitz AT, Gabizon A. Comparative study of the antitumor activity of free doxorubicin and polyethylene glycol-coated liposomal doxorubicin in a mouse lymphoma model. *Clin Cancer Res* 1998, **4**, 499–505.
14. Muggia FM, Hainsworth J, Jetters S, *et al*. Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. *J Clin Oncol* 1997, **15**, 987–993.
15. Uziely B, Jeffers S, Isacson R, *et al*. Liposomal doxorubicin: antitumor activity and unique toxicities during two complementary phase I studies. *J Clin Oncol* 1995, **13**, 1777–1785.
16. Northfelt DW, Dezube BJ, Thommes JA, *et al*. Pegylated liposomal doxorubin versus doxorubicin, bleomycin and vincristine in the treatment of severe AIDS-related Kaposi's sarcoma. *J Clin Oncol* 1998, **16**, 683–691.
17. Berry G, Billingham M, Alerman E, *et al*. The use of cardiac biopsy to demonstrate reduce cardiotoxicity in AIDS Kaposi's sarcoma patients treated with pegylated liposomal doxorubicin. *Ann Oncol* 1998, **9**, 711–716.
18. Safra T, Muggia FM, Jeffers S, *et al*. Pegylated liposomal doxorubicin (Doxil) reduced clinical cardiotoxicity in patients reaching or exceeding 500 mg/m^2 cumulative doses of Doxil. *Proc Am Soc Clin Oncol* 2000, **19**, 206a.
19. Radice P, Jahanzeb M, Koletsky A, *et al*. Weekly pegylated liposomal doxorubicin (PEG-LD) is extremely well tolerated as second line chemotherapy. *Proc Am Soc Clin Oncol* 1999, **18**, 520.
20. Schwonzen M, Kurbacher C, Mallmann P. Liposomal doxorubicin and weekly paclitaxel in the treatment of metastatic breast cancer. *Anticancer Drugs* 2000, **11**, 681–685.
21. Woll PJ, Carmichael J, Chan S, *et al*. Phase II study, results on safety and efficacy of Caelyx (Doxil) in combination with paclitaxel in treatment of metastatic breast cancer. *Eur J Cancer* 1999, **35**(Suppl. 4), 322.
22. Moore MR, Srinivasiah J, Feinberg BA. Phase II randomized trial of doxorubicin plus paclitaxel (AT) versus doxorubicin HCL liposome injection (Doxil) plus paclitaxel (DT) in metastatic breast cancer. *Proc Am Soc Clin Oncol* 1998, **17**, 160.
23. Jones V, Finucane D, Rodriguez R, Saleti F, Espinoza M, Gutheil JC. Phase II study of weekly paclitaxel (Taxol) and liposomal doxorubicin (Doxil) in patients with locally advanced and metastatic breast cancer. *Proc Am Soc Clin Oncol* 2000, **19**, 116a.
24. Lopez F, Sikov W. Phase I studies of weekly docetaxel with Doxil or weekly doxorubicin. *Proc Am Soc Clin Oncol* 2000, **19**, 213a.
25. Sparana JA, Malik U, Rajdev L, Sarta C, Hopkins U, Wolff A. Phase I trial of liposomal doxorubicin and docetaxel in advanced breast cancer. *J Clin Oncol* 2001, **19**, 3117–3125.
26. Holmes FA, Madden T, Newman RA, *et al*. Sequence dependent alteration of doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 1996, **14**, 2713–2721.
27. Briasoulis E, Tzamakou E, Rammou D. Phase I trial and interaction pharmacokinetics of PEG-liposomal doxorubicin and weekly taxol. *Br J Cancer* 1999, **80**(Suppl. 2), 63.
28. Israel VK, Jeffers S, Bernal G, *et al*. Phase I study of Doxil (liposomal doxorubicin) in combination with paclitaxel. *Proc Am Soc Clin Oncol* 1997, **17**, 239a.
29. Muggia FM, Hornreich G, Wadler S, *et al*. Overview of toxicities from a combination of Doxil-paclitaxel (PacliDox) in a New York Gynecologic Oncology Group (NYGOG) study on endometrial carcinomas and sarcomas. *Proc Am Soc Clin Oncol* 1999, **18**, 380a.
30. National Cancer Institute. *Guidelines for Reporting Adverse Drug Reactions*. Bethesda, MD, Division of Cancer Treatment. National Cancer Institute, 1978.
31. World Health Organization. *Handbook for Reporting Results of Cancer Treatment*. *WHO Offset Publication No. 48*. Geneva, World Health Organization, 1979.
32. Treat J, Greenspan A, Forst D. Antitumor activity of liposome encapsulated doxorubicin in advanced breast cancer: phase II study. *J Natl Cancer Inst* 1990, **82**, 1706–1710.
33. Rahman A, Treat J, Roth JK, *et al*. A phase I clinical trial and pharmacokinetic evaluation of liposome encapsulated doxorubicin. *J Clin Oncol* 1990, **8**, 1093–1100.
34. Gabizon A, Catane R, Uziely B, *et al*. Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polytheneglycol-coated liposomes. *Cancer Res* 1994, **54**, 987–992.
35. Amantea M, Newman MS, Sullivan TM, Forrest A, Working PK. Relationship of dose intensity to the induction of palmar-plantar erythrodysesthesia by pegylated liposomal doxorubicin in dogs. *Hum Exp Toxicol* 1999, **18**, 17–26.
36. Lyass O, Uziely B, Ben-Yosef R, *et al*. Correlation of toxicity with pharmacokinetics of pegylated liposomal doxorubicin (Doxil) in metastatic breast carcinoma. *Cancer* 2000, **89**, 1037–1047.
37. Hubert A, Lyass O, Pode D, Gabizon A. Doxil (Caelyx): an exploratory study with pharmacokinetics in patients with hormone-refractory prostate cancer. *Anticancer Drugs* 2000, **11**, 123–127.