available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Phase 1 European Organisation for Research and Treatment of Cancer study determining safety of pegylated liposomal doxorubicin (Caelyx®) in combination with ifosfamide in previously untreated adult patients with advanced or metastatic soft tissue sarcomas

O.S. Nielsen[a,], P. Reichardt[b], T.B. Christensen[a], D. Pink[b], S. Daugaard[c], C. Hermans[d], S. Marreaud[d], M. van Glabbeke[d], J. Blay[e], I. Judson[f]*

[a]*Aarhus University Hospital, Department of Oncology, Nörrebrogade 44, DK-8000 Aarhus C, Denmark*
[b]*Charité Campus Buch, HELIOS-Klinikum Berlin-Buch, Department of Hematology and Oncology, Berlin, Germany*
[c]*Rigshospitalet, Department of Pathology, Copenhagen, Denmark*
[d]*EORTC, Data Center, Brussels, Belgium*
[e]*Unite Cytokines et Cancers, Centre Leon Berard, Lyon, France*
[f]*Royal Marsden Hospital, Department of Oncology, London, UK*

ARTICLE INFO

Article history:
Received 5 April 2006
Accepted 7 April 2006
Available online 7 August 2006

Keywords:
Caelyx®
Doxorubicin
Ifosfamide
Phase 1
Chemotherapy
Soft tissue sarcoma

ABSTRACT

This phase I study evaluated the toxicity of first-line combined pegylated liposomal doxorubicin (Caelyx®) and ifosfamide in patients with advanced and/or metastatic soft tissue sarcomas. Five dose levels (L) were studied: Caelyx® 30 mg/m^2 (L1–4) or 40 mg/m^2 (L5) 1-h infusion d 1 q 3 weeks + ifosfamide and mesna at *X* g/m^2/4 h d 1–3 q 3 weeks at five doses: L1: *X* = 1.7 g; L2: *X* = 2 g; L3: *X* = 2.5 g; L4 and L5: *X* = 3 g. Cohorts of 3 patients were entered at each level unless a dose-limiting toxicity (DLT) occurred. In case of DLT in 1 of 3 patients a new cohort was added. Toxicity was evaluated by Common Toxicity Criteria (CTC). A total of 28 patients was included: 4 at dose L1, 8 at L2, 3 at L3, 6 at L4, and 7 at L5. Median age was 60 years (range 29–69 years). Male/female ratio was 12/16. Seventy-five percent of patients had a performance status of 1.0 and 36% had leiomyosarcomas. No DLT was observed at dose L1–4. Six patients developed a DLT at dose L5, and thus the recommended dose is level 4 (i.e. Caelyx® 30 mg/m^2/1 h d 1 + ifosfamide at 3 g/m^2/4 h d 1–3 q 3 weeks). Few haematological and biochemical events were observed and the principal toxicities were granulocytopaenia and leucopaenia. Five patients discontinued therapy because of toxicity, 4 of them at dose level 5. Non-haematological toxicities > grade 2 were also few. Palmar-plantar erythrodysesthesia (PPE) > grade 1 was not seen. Two patients obtained partial response (PR) and 13 stable disease (SD). Median overall survival (OS) was 333 d and median progression-free survival (PFS) 174 d. In conclusion, this seems to be a feasible combination in patients with advanced soft tissue sarcomas, allowing ifosfamide to be given in a dosage similar to that used when given alone. The recommended dose for future studies is Caelyx® 30 mg/m^2/1 h d 1 + ifosfamide 3 g/m^2/4 h d 1–3 q 3 weeks.

* *Corresponding author:* Tel.: +4589492555; fax: +45 89492550.
E-mail address: osnie@as.aaa.dk (O.S. Nielsen).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.04.011

1. Introduction

Chemotherapy for patients with advanced soft tissue sarcomas is inadequate at present and prolongation of overall survival has not been demonstrated with combination chemotherapy as compared with single agent chemotherapy.[1–3] Few drugs have significant activity in soft tissue sarcomas and combination chemotherapy is only slightly more active at the expense of increased toxicity. Doxorubicin and ifosfamide are the most active agents,[3,4] but doxorubicin treatment is limited because of cumulative cardio-toxicity.[5] Unfortunately, none of the other tested anthracycline analogues have shown superiority or comparability to doxorubicin in terms of therapeutic activity and toxicity.[3,4,6–8] Numerous other new drugs have been tested, both as first- and second-line chemotherapy, but unfortunately few show activity of clinical importance.[3] New drugs are therefore needed in the treatment of soft tissue sarcomas.

In a randomised phase II trial by the European Organisation for Research and Treatment of Cancer (EORTC), Caelyx® (pegylated liposomal doxorubicin) was found to have equivalent activity to doxorubicin in soft tissue sarcomas, with an improved toxicity profile, especially with regards to reduced myelosuppression.[9] The Italian Sarcoma Group reached a similar conclusion.[10] Caelyx® therefore deserves to be investigated further in soft tissue sarcomas. Its lack of myelosuppression also suggests that the combination of Caelyx® with ifosfamide should be explored further in the treatment of soft tissue sarcomas. Many uncontrolled prospective trials have evaluated the effect of combined doxorubicin and ifosfamide. Three randomised trials are available, which compared doxorubicin or doxorubicin-based chemotherapy with combined doxorubicin and ifosfamide.[11–13] Two demonstrated a statistically significant higher response rate for the combined treatment but no survival advantage.[11,12] The third study did not show either a survival or a response benefit.[13] There is also evidence, mainly from uncontrolled studies, that the dose of the anthracycline and ifosfamide may play a role, though this is hardly confirmed by large studies on the whole population with advanced soft tissue sarcomas. However, if higher doses of either or both drugs could be administered it is likely that an improved effect could be expected. Combining ifosfamide with Caelyx® instead of doxorubicin should theoretically allow the safe administration of a higher dose of ifosfamide and it is hoped thereby result in improved activity. Hence it seems worthwhile to evaluate the effect of combined ifosfamide and Caelyx® in advanced soft tissue sarcomas.

The present phase I study tested the possibility of giving both drugs at therapeutic doses, by increasing the dose of ifosfamide and keeping the dose of Caelyx® fixed. The starting dose was based on data from the study on ovarian cancer.[14] However, the treatment was modified and given with a 3-week schedule according to the standard schedule of ifosfamide, as used for sarcomas by the EORTC.

2. Patients and methods

The trial was an open-label, non-randomised phase I study. The EORTC Soft Tissue and Bone Sarcoma Group conducted the study in two sarcoma centres: Aarhus (Denmark) and Berlin (Germany).

2.1. Patients

Patients with histologically confirmed soft tissue sarcoma and with measurable lesions with evidence of progression within 6 weeks prior to treatment were eligible for the study. GIST and embryonal rhabdomyosarcomas were not included. Patient age was between 18 and 70 years. Patients with prior malignant disease or other serious medical conditions were excluded. Patients were required to have normal haematological function (white blood cell count (WBC) $\geqslant 4 \times 10^9/1$ and platelets $\geqslant 100 \times 10^9/1$), serum creatinine $\leqslant 120$ μmol/l or calculated clearance (Cockroft and Gault method) >65 ml/min, bilirubin <30 μmol/l, albumin $\geqslant 25$ g/l, cardiac ejection fraction $\geqslant 50\%$ as determined by echocardiograhic or isotopic methods. Further inclusion criteria were: World Health Organisation (WHO) performance status 0 or 1, no radiotherapy to the sole index lesion, and no previous chemotherapy for advanced disease. The study was performed in accordance with the Declaration of Helsinki and local ethics regulations. Written informed consent was obtained.

2.2. Dose levels studied

Caelyx® was supplied by Schering-Plough in vials as a liquid each containing 20 mg of doxorubicin hydrochloride at a concentration of 2.0 mg/ml (stored at 2–8 °C). Five dose levels were studied: Caelyx® 30 mg/m^2 (level 1–4) or 40 mg/m^2 (level 5) 1-h infusion d 1 q 3 weeks + ifosfamide with mesna at *X* g/m^2 4-h infusion d 1–3 q 3 weeks at 5 doses: Level 1: *X* = 1.7 g; level 2: *X* = 2 g; level 3: *X* = 2.5 g; level 4 and 5: *X* = 3 g. Mesna 600 mg/m^2 was given as an intravenous bolus directly before the ifosfamide infusion. The ifosfamide and mesna infusion was followed daily by a further 1.2 g/m^2 mesna at 4 h and 8 h. Sufficient diuresis was established before treatment by prehydration with 1000 ml dextrose saline over 2 h and 500 ml 20% mannitol over 30 min. To prevent severe acidosis the patients received 150–180 mmol intravenous sodium bicarbonate daily during the 3-d ifosfamide infusion and the day after. Anti-emetics were given in accordance with local practice.

2.3. Dose escalation

Successive cohorts of 3 patients were entered at each dose level unless a dose-limiting toxicity (DLT) occurred, defined as absolute neutrophil count (ANC) $<0.5 \times 10^9$ lasting for 7 d or for 3 d + fever (=38.5 °C), grade 4 thrombocytopenia, any grade 3–4 toxicity except nausea, vomiting and alopecia, and any toxicity requiring a 2-week delay. If no DLT was observed amongst the 3 patients, the dose was escalated to the next dose level. In case of DLT in 1 out of 3 patients a new cohort of 3 patients was added. The recommended dose was defined as one dose level below the maximum tolerated dose (MTD). Patients developing a DLT could continue treatment at one dose level lower after discussion with the study coordinator. Patients that thereafter still developed serious toxicity went

off-study and were offered ifosfamide. Patients having haematopoietic toxicity on d 1 of treatment not defined as a DLT but neither allowing full-dose treatment were delayed 1 week. If, at that time, treatment was still not possible, the treatment was delayed 1 week more. If treatment after 2 weeks was still not possible the event was recorded as DLT and the patient continued treatment at one dose level lower. The definition of haematopoietic toxicity resulting in 1-week delay was WBC $<2\times10^9$/l or ANC $<1\times10^9$/l and platelets $<80\times10^9$/l.

2.4. Toxicity evaluation

Follow-up studies included assessment of haematology and biochemistry before each cycle of treatment. Creatinine clearance was determined prior to all treatments. Treatment was administered up to a maximum of six cycles of chemotherapy or until documented disease progression, unacceptable toxicity, or patient refusal. If progression occurred before the first formal disease evaluation (6 weeks after treatment start), the treatment was discontinued and the response to treatment was assessed as 'early progression'. In case of stabilisation of the disease and absence of unacceptable toxicity, the patient was treated for a minimum of two cycles. Thereafter, the decision to continue the treatment until disease progression or a maximum of six cycles was left to the responsible investigator. In case of objective (complete or partial) response, the treatment was continued until documented disease progression or a maximum of six cycles. Whatever the disease status, the treatment was always discontinued in case of patient refusal, excessive toxicity precluding further therapy, or incoming new safety information from the sponsor.

2.5. Statistics

Toxicity was assessed separately for each cycle of therapy using National Cancer Institute Common Toxicity Criteria (NCI-CTC). Response to treatment was assessed every 6 weeks until documented progression using Response Evaluation Criteria in Solid Tumours (RECIST). Responses were subject to independent peer-review. The patients were followed until progression, in the absence of any further anti-cancer treatment. Progression-free survival (PFS) and overall survival (OS) were calculated by use of the Kaplan–Meier method.

3. Results

3.1. Patient characteristics and doses administered

Between March 2002 and November 2004 a total of 28 patients were enrolled in the study by two centres: 17 patients from Berlin and 11 patients from Aarhus. Median age was 60 years (age range 29–69 years). All patients were included in the toxicity analysis. One patient did not have haematological and biochemistry assessment performed according to the protocol, but available data showed that this patient had dose-limiting thrombocytopenia. This patient is included in all analyses. Five patients were not evaluable for response because they had received only one cycle of treatment. Two other patients progressed after one cycle and were therefore evaluable for response.

Patient characteristics are given in Table 1. Seventy-five percent of the patients had a WHO performance status of 1. In approximately one-third of the patients the histological type was leiomyosarcoma. The majority of patients had extremity sarcomas. Patient characteristics were similar in the dose groups (data not shown). Four patients were included at dose level 1, 8 patients at level 2, 3 patients at level 3, 6 patients at level 4, and 7 patients at level 5.

3.2. Treatment and toxicity

The number of documented cycles and patient distribution by dose level is listed in Table 2. The following numbers of additional patients were included at each dose level: dose level 1 –1 patient added due to early progressive disease (PD); dose level 3: 5 patients due to early PD and patient refusal; dose level 4: 3 patients due to early PD; dose level 5: 4

Table 1 – Patient characteristics

	n	%
Total	28	
Eligible for response	23	82
Eligible for toxicity	28	
Gender		
Male	12	43
Female	16	57
WHO performance status		
0	7	25
1	21	75
Histology		
Leiomyosarcoma	8	32
Synovial sarcoma	2	8
Rhabdomyosarcoma	1	4
Fibrosarcoma	1	4
Malignant peripheral nerve sheath tumour	1	4
MFH	1	4
MPNST	1	4
Angiosarcoma	1	4
Pleomorphic epitheloid	1	4
Undifferentiated sarcoma	1	4
High-grade sarcoma (NOS)	7	28
Localisation		
Thorax	4	14
Retro/intra abdomen	5	18
Lower extremity	12	43
Upper extremity.	3	11
GU visceral	1	4
GI visceral	2	7
GY visceral	1	4
Prior treatments		
Surgery	25	89
Radiotherapy	7	25
Adjuvant chemotherapy	1	4

WHO, World Health Organisation; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumour; NOS, none otherwise specified; GU, genito-urinary; GI, gastrointestinal; GY, gynecological.

Table 2 – Number of documented cycles and number of patients at the five dose levels

Cycle number	Dose level 1 Patients (*n*)	Dose level 2 Patients (*n*)	Dose level 3 Patients (*n*)	Dose level 4 Patients (*n*)	Dose level 5 Patients (*n*)	Total patients (*n*)
1	1	3	1		2	7
2				3	1	4
3		1			3	4
4		1		1	1	3
5	1					1
6	2	3	2	2		9
Total patients (*n*)	4	8	3	6	7	28
Total no. cycles	18	28	13	22	17	98

Table 3 – Reported dose limiting toxicities (DLT)

Dose level	Patients (*n*)	Toxicity
5	1	Dyspnoea + allergic reaction
5	1	Thrombocytopenia + renal insufficiency
5	3	Febrile neutropaenia
5	1	Thrombocytopenia

DLT was not observed at dose level 1–4.

patients due to toxicity. Nine patients completed the six cycles of therapy (Table 2). One was taken off protocol therapy for progression, but no objective progression was reported. Six other patients discontinued therapy because of progression. Four patients refused further treatment. Five patients discontinued therapy because of toxicity (4 of them treated at the last dose level). The patient who discontinued therapy because of febrile neutropaenia in the first cohort was not considered as a DLT. Two patients who had DLT were taken off protocol therapy for reasons other than toxicity, i.e. 'doctor decision' and refusal.

No DLT was observed at levels 1–4. Six patients with DLT were observed at level 5 (Table 3). The recommended dose level is thus level 4, i.e. Caelyx® 30 mg/m^2/1-h day 1 + ifosfamide (with mesna) at 3 g/m^2/4-h day 1–3 q 3 weeks.

Toxicities at dose level 1–3; dose level 4 (recommended dose) and dose level 5 (maximum tolerated dose; MTD) are shown in Tables 4 and 5. Few haematological and biochemical events were observed and primarily granulocytopaenia and leucopaenia (Table 4). Non-haematological toxicities > grade 2 were also few (Table 5). Palmar-plantar erythrodysesthesia (PPE) > grade 1 was not seen.

3.3. *Response*

Among 23 patients eligible for response, 2 obtained a partial response (PR) at dose level 5 and for 16 patients the best response was stable disease (SD) (overall response rate 9%). The median PFS was 174 d and the median OS was 333 d (Fig. 1). Currently, 4 patients are still alive and progression-free and 5 patients are still alive but have progressed. All deaths were due to progression.

So far, all but 1 of the alive and progression-free patients have been treated at dose level 4 and 5, but this may simply reflect the fact that follow-up was shorter for those patients most recently entered into the trial. Although the trial was not powered for any formal comparison between therapeutic groups, illustrative survival and PFS curves by dose level do not suggest any differences between the dose groups (data not shown).

4. Discussion

Caelyx® is a form of doxorubicin in which the drug is encapsulated in liposomes coated in polyethylene glycol (stealth liposomes). These are less readily eliminated by the reticulo–endothelial system, resulting in a long circulation lifetime.[15,16] Extravasation of liposomes through the relatively leaky tumour vasculature into the tumour interstitial spaces may result in targeting of drug to tumour, relative to normal tissue, thus offering a potential therapeutic benefit.[17] However, it also has a drawback due to accumulation in the skin giving rise to so-called palmar-plantar erythrodysesthesia (PPE). Apart from mucositis the other toxicities of Caelyx®, including cardio-toxicity, are less than those of conventional doxorubicin. Thus it is obvious that Caelyx® could be an attractive alternative to doxorubicin in soft tissue sarcomas.

Table 4 – Haematological toxicities at dose level 1–3, level 4 (recommended dose) and level 5 (maximum tolerated dose; MTD)

	Dose level 1–3		Dose level 4		Dose level 5	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Leucopaenia	3	8	0	2	1	5
Granulocytopaenia	0	6	1	2	0	4
Thrombocytopenia	1	0	0	0	0	2
Anaemia	4	0	0	0	1	0

Only grade 3 and 4 toxicities are shown. Number of patients at each grade.

Table 5 – Selected non-haematological toxicities at dose level 1–3, level 4 (recommended dose) and level 5 (dose-limiting toxicity; DLT)

	Dose level 1–3		Dose level 4		Dose level 5	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Allergy	1	0	0	0	1	1
Arrhythmia	1	0	0	0	0	0
Fatigue	3	0	0	0	0	0
Fever	1	0	0	0	0	0
Rash	1	0	0	0	0	0
Nausea	0	0	0	0	1	0
Vomiting	0	0	0	0	1	0
Other GI	1	0	0	0	0	0
Febrile neutropaenia	4	0	0	0	4	1
Infection	1	0	0	0	0	0
Dyspnoea	3	1	0	0	0	1

Only grade 3 and 4 toxicities are shown. Number of patients at each grade.
GI, gastrointestinal.

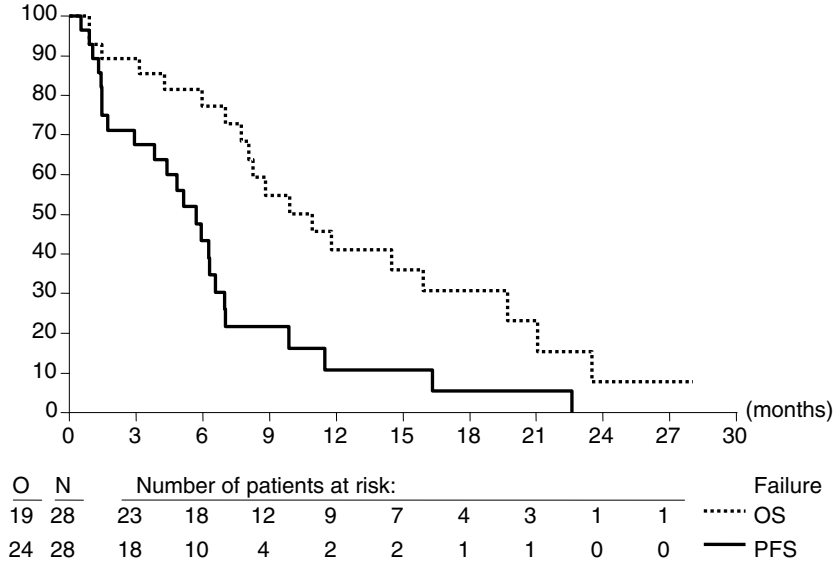

Fig. 1 – Observed events (O), number of patients (N), overall survival (OS) and progression-free survival (PFS) (all patients).

However, at present, the clinical use of Caelyx® in soft tissue sarcomas is still limited. Although a number of studies have demonstrated equivalent activity of Caelyx® and doxorubicin in soft tissue sarcomas, its anti-tumoural effectiveness is not expected to be better than that of doxorubicin.[3,9,10,18–21] Neither did Caelyx® induce any remissions in patients progressing under a doxorubicin-containing regimen.[22] In the present study the response rate was not impressive (overall response rate 9%) and responders were only observed at the MTD. Recently it has been indicated that combined pegylated-liposomal doxorubicin and paclitaxel may be active in angiosarcomas,[23] but further data are needed. In addition, the improved toxicity profile of Caelyx® is probably counterbalanced by the fact that it is far more expensive than conventional doxorubicin.

At the time of initiating the present study, the feasibility of the combination of ifosfamide and Caelyx® had been tested in recurrent ovarian cancer.[14] In this combined phase I and II study ifosfamide 1.8 g/m^2 d 1–3 was combined with Caelyx® 25–30–35–40 mg/m^2 d 1 every 4 weeks. Interestingly, despite the fact that patients had had prior chemotherapy, a MTD was not reached in this study. The combination was feasible and, in general, the toxicity was low. In breast cancer a study that combined Caelyx® 30 mg/m^2 and cyclophosphamide 600 mg/m^2 q 3 weeks also showed moderate toxicity.[24,25] Importantly 70% of the patients had received prior chemotherapy and/or radiotherapy. In addition to ifosfamide, Caelyx® has also been combined with other drugs, such as gemcitabine, paclitaxel, topotecan and vinorelbine, and for most of these combinations the DLT was myelosuppression.[25–31]

In the present phase I dose-finding study, the feasibility of giving Caelyx® in combination with ifosfamide in soft tissue sarcomas was evaluated to test the possibility of giving both drugs at therapeutic doses. This study demonstrated that this combination was feasible in patients with advanced soft tissue sarcomas, allowing ifosfamide to be given in a dosage similar to that used when given alone. However, if combination chemotherapy is indicated in soft tissue sarcomas most

centres still use ifosfamide and conventional doxorubicin as their standard treatment regimen, often in high doses with haematopoietic growth factor support. An EORTC study is currently investigating whether intensive combination chemotherapy with ifosfamide (2.5 g/m^2 d 1–4) and doxorubicin (25 mg/m^2 d 1–3) with haematopoietic growth factor support is superior to doxorubicin alone (75 mg/m^2 d 1) in patients with advanced soft tissue sarcomas. If this study demonstrates superiority for the combination, and that the toxicity of the combination is acceptable and manageable, this may hamper further introduction of combined Caelyx® and ifosfamide. If, on the other hand, toxicity is a problem, this may mean that Caelyx® still has a future in this disease and that further phase II and III studies should be performed. In addition, combined Caelyx® and ifosfamide may also be a good alternative in patients with cardiac or other health-related problems that contradict the use of combined doxorubicin and ifosfamide. Also, if cardio-toxicity in long-term survivors tends to be a problem, this may further argue for the use of Caelyx® instead of conventional doxorubicin. Owing to the poor prognosis of advanced sarcomas, this is likely to be an issue only when doxorubicin is used in the adjuvant setting. Based on the present phase I study, the recommended dose is Caelyx® 30 mg/m^2/1-h d 1 and ifosfamide (with mesna) at 3 g/m^2/4-h d 1–3 q 3 weeks.

In conclusion, the present phase I trial showed that Caelyx® and ifosfamide is a feasible combination in patients with advanced soft tissue sarcomas, allowing administration of ifosfamide at a dosage similar to that used when given alone.

Conflict of interest statement

None declared.

Acknowledgement

This paper was presented in October 2005 at ECCO 13, Paris, France.

REFERENCES

1. Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localized resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *Lancet* 1997;**350**:1647–54.
2. O'Byrne K, Steward WP. The role of chemotherapy in the treatment of adult soft tissue sarcomas. *Oncology* 1999;**56**:13–23.
3. Nielsen OS, Blay JY, Judson IR, van Glabbeke M, Verweij J, van Oosterom AT. Metastatic soft tissue sarcoma in adults: prognosis and treatment options. *Am J Cancer* 2003;**2**:211–21.
4. Verweij J, Mouridsen HT, Nielsen OS, et al. The present state of the art in chemotherapy for soft tissue sarcomas in adults: the EORTC point of view. *Critical Rev Oncol/Hematol* 1995;**20**:193–201.
5. Launchbury AP, Habboubit N. Epirubicin and doxorubicin: a comparison of their characteristics, therapeutic activity and toxicity. *Cancer Treatm Rev* 1993;**19**:197–228.
6. Bramwell VHC, Mouridsen HT, Mulder JH, et al. Carminomycin vs. adriamycin in advanced soft tissue sarcomas: an EORTC randomized phase II study. *Eur J Cancer Clin Oncol* 1983;**19**:1097–104.
7. Bull FE, von Hoff DD, Balcerak SP, Stephens RL, Panettiere FJ. Phase II trial of mitoxantrone in advanced sarcomas: a Southwest Oncology Group study. *Cancer Treat Reports* 1985;**69**:231–3.
8. Nielsen OS, Dombernowsky P, Mouridsen H, et al. Epirubicin is not superior to doxorubicin in the treatment of advanced soft tissue sarcomas. The experience of the EORTC soft tissue and bone sarcoma group. *Sarcoma* 2000;**4**:31–5.
9. Judson I, Radford JA, Harris M, et al. Randomized phase II trial of pegylated liposomal doxorubicin (Doxil®/Caelyx®) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2001;**37**:870–7.
10. Toma S, Tucci A, Villani G, Carteni G, Spadini N, Palumbo R. Liposomal doxorubicin (Caelyx) in advanced pretreated soft tissue sarcomas: a phase II study of the Italian Sarcoma Group (ISG). *Anticancer Res* 2000;**20**:485–91.
11. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol* 1993;**11**:1276–85.
12. Edmonson JH, Ryan LM, Blum RH, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol* 1993;**11**:1269–75.
13. Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus cyvadic versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 1995;**13**:1537–45.
14. Bourgeois H. Pegylated liposomal doxorubicin (Caelyx) and ifosfamide in recurrent ovarian cancer (ROC): a phase I/II Gineco study. *Proc ASCO* 2000;**18**:398a.
15. Lasic DD. Doxorubicin in sterically stabilized liposomes. *Nature* 1996;**380**:561–2.
16. Vaage J, Barbera-Guillem E, Abra R, Huang A, Working P. Tissue distribution and therapeutic effect of intravenous free or encapsulated liposomal doxorubicin on human prostate carcinoma xenografts. *Cancer* 1994;**73**:1478–84.
17. Northfelt DW, Dezube BJ, Thommes JA, et al. Efficacy of pegylated-liposomal doxorubicin in the treatment of AIDS-related Kaposi's sarcoma after failure of standard chemotherapy. *J Clin Oncol* 1997;**15**:653–9.
18. Siehl JM, Thiel E, Schmittel A, et al. Ifosfamide/liposomal daunorubicin is a well tolerated and active first-line chemotherapy regimen in advanced soft tissue sarcoma: results of a phase II study. *Cancer* 2005;**104**:611–7.
19. Bafaloukos D, Papadimitriou C, Linardou H, et al. Combination of pegylated liposomal doxorubicin (PLD) and paclitaxel in patients with advanced soft tissue sarcoma: a phase II study of the Hellenic Cooperative Oncology Group. *Br J Cancer* 2004;**91**:1639–44.
20. Skubitz KM. Phase II trial of pegylated-liposomal doxorubicin (Doxil) in sarcoma. *Cancer Invest* 2003;**21**:167–76.
21. Sutton G, Blessing J, Hanjani P, Kramer P. Gynecologic Oncology Group. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol* 2005;**96**:749–52.
22. Poveda A, Lopez-Pousa A, Martin J, et al. Phase II clinical trial with pegylated liposomal doxorubicin (Caelyx/Doxil) and quality of life evaluation (EORTC QLQ-C30) in adult

patients with advanced soft tissue sarcomas. *Sarcoma* 2005;**9**:127–32.
23. Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. *Cancer* 2005;**104**:361–6.
24. Ranson MR, Carmichael J, O'Byrne K, Stewart S, Smith D, Howell A. Treatment of advanced breast cancer with sterically stabilized liposomal doxorubicin: results of a multicenter phase II trial. *J Clin Oncol* 1997;**15**:3185–91.
25. Ranson MR, Cheeseman S, White S, Margison J. Caelyx (stealth liposomal doxorubicin) in the treatment of advanced breast cancer. *Crit Rev Oncol Hematol* 2001;**37**:115–20.
26. Alberts DS, Muggia FM, Carmichael J, et al. Efficacy and safety of liposomal anthracyclines in phase I/II clinical trials. *Semin Oncol* 2004;**31**:53–90.
27. Rivera E. Current status of liposomal anthracycline therapy in metastatic breast cancer. *Clin Breast Cancer* 2003;**4**:S76–83.
28. Rivera E, Valero V, Arun B, et al. Phase II study of pegylated liposomal doxorubicin in combination with gemcitabine in patients with metastatic breast cancer. *J Clin Oncol* 2003;**21**:3249–54.
29. Schwonzen M, Kurbacher CM, Mallmann P. Liposomal doxorubicin and weekly paclitaxel in the treatment of metastatic breast cancer. *Anticancer Drugs* 2000;**11**: 681–5.
30. Ryan CW, Fleming GF, Janisch L, Ratain MJ. A phase I study of liposomal doxorubicin (Doxil) with topotecan. *Am J Clin Oncol* 2000;**23**:297–300.
31. Burstein HJ, Ramirez MJ, Petros WP, et al. Phase I study of doxil and vinorelbine in metastatic breast cancer. *Ann Oncol* 1999;**10**:1113–6.