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Randomised 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

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Abstract

CAELYX®/DOXIL®, pegylated liposomal doxorubicin, has shown antitumour activity and reduced toxicity compared with standard doxorubicin in other tumour types. In this prospective randomised trial, 94 eligible patients with advanced soft-tissue sarcoma (STS) were treated, 50 with CAELYX® (50 mg/m^2 by a 1 h intravenous (i.v.) infusion every 4 weeks) and 44 with doxorubicin (75 mg/m^2 by an i.v. bolus every 3 weeks). Histological subtypes were evenly matched, 33% were leiomyosarcoma (CAELYX®: 18; doxorubicin: 13). Primary disease sites were well matched. CAELYX® was significantly less myelosuppressive, only 3 (6%) patients had grade 3 and 4 neutropenia, versus 33 (77%) on doxorubicin; febrile neutropenia occurred in 7 (16%) patients given doxorubicin, but only 1 (2%) given CAELYX®. 37 (86%) patients on doxorubicin had grade 2–3 alopecia, but only 3 (6%) on CAELYX®, and the major toxicity with CAELYX® was to the skin. Palmar-plantar erythrodysesthesia with CAELYX® was grade 1: 4 (8%) patients, grade 2: 11 (22%) patients, grade 3: 9 (18%) patients and grade 4: 1 (2%) patient. Other non-haematological grade 3 and 4 toxicities were rare. Confirmed responses were observed with both agents: CAELYX®: complete response (CR) 1 (uterine), partial response (PR) 4 (response rate (RR) 10%); and doxorubicin: CR 1, PR 3 (RR of 9%); with the best response being stable disease (NC) in 16 and 18 patients, respectively. The reason for the low response rate is unknown, but it may be due partly to a high proportion of gastrointestinal stromal tumours. In conclusion, CAELYX® has equivalent activity to doxorubicin in STS with an improved toxicity profile and should be considered for further investigation in combination with other agents such as ifosfamide.

Keywords: Soft-tissue sarcoma; Doxorubicin; Liposomal doxorubicin

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1. Introduction

Chemotherapy of adult soft-tissue sarcoma (STS) is presently unsatisfactory with only two agents reliably demonstrating significant activity, i.e. doxorubicin [1] and ifosfamide [2]. There appears to be a dose–response relationship for both agents, but randomised trials have so far failed to show a benefit for dose intensification using haemopoietic growth factors support [3]. Similarly, a three-way randomised trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) did not show a significant benefit in terms of progression-free or overall survival for combination chemotherapy with respect to single agent doxorubicin [4]. For this reason, single agent doxorubicin has been taken as the most logical comparator for studies involving new agents in the treatment of these tumours [1,5].

Doxorubicin treatment is limited by bone marrow suppression and cumulative cardiotoxicity. A new form of doxorubicin has been developed in which the drug is encapsulated in liposomes which have been modified by the addition of polyethylene glycol (PEG) [6]. These sterically hindered STEALTH® liposomes, when carrying doxorubicin, are known as CAELYX® or DOXIL®. They have the advantage over unmodified liposomes that they are less readily eliminated by the reticuloendothelial system resulting in a long circulation half-life of approximately 50 h in man. Extravasation of liposomes through the relatively leaky tumour vasculature into the tumour interstitial spaces results in a level of targeting of the drug to the tumour relative to normal tissue which has been observed in animal models [7] leading to activity in refractory human tumours [8,9]. Although accumulation of the drug in the tumour is of potential value, there is also accumulation in the skin necessitating a greater dose interval than is usual for doxorubicin, e.g. 4 weeks [10].

Phase I trials of CAELYX® have shown reduced alopecia and myelosuppression compared with conventional doxorubicin and also a reduction in cardiotoxicity [9,10]. Skin toxicity and to a lesser extent bone marrow suppression was dose limiting. The skin toxicity consists of reddening and pain in the palms of the hands, soles of the feet, skin creases and pressure points and has been termed palmar-plantar erythrodysesthesia (PPE). Phase II studies have been carried out using a range of doses and dosing intervals. Treatment every 3 weeks resulted in unacceptable levels of skin toxicity but, with a 4 week interval, doses in the range 40–60 mg/m^2 can be given [10]. Antitumour activity has been reported in refractory ovarian cancer and Kaposi's sarcoma [8,9].

In this study, patients with advanced or metastatic adult STS were randomised to receive either CAELYX® 50 mg/m^2 every 4 weeks by intravenous (i.v.) infusion or doxorubicin 75 mg/m^2 by i.v. bolus injection every 3 weeks. The end-points of the study were response rate, response duration and toxicity.

2. Patients and methods

2.1. Eligibility

Patients had to meet the following inclusion criteria: (1) histologically confirmed diagnosis of one of the following sarcoma types — malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, synovial sarcoma, malignant paraganglioma, fibrosarcoma, leiomyosarcoma, including haemangiopericytoma, neurogenic sarcoma, unclassified sarcoma, miscellaneous sarcoma including mixed mesodermal tumours of the uterus; (2) no prior chemotherapy; (3) at least one bidimensionally measurable lesion of $\geqslant$2.5 cm in diameter or $\geqslant$2 cm in the case of lung metastases and progressive disease in the previous 4 weeks; (4) World Health Organization (WHO) performance status $\leqslant$2; (5) cardiac ejection fraction within normal limits; (5) adequate bone marrow function, i.e. haemoglobin $\geqslant$10 g/l, neutrophils $\geqslant 2.0\times10^9$/l platelets $\geqslant 100\times10^9$/l; (6) adequate organ function as defined by creatinine $\leqslant$140 μmol/l and bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $<1.25\times$ upper limit of normal unless related to cancer; (7) metastatic a disease or locally advanced disease not amenable to curative surgery; (8) age $\geqslant$18 years; (9) use of adequate contraception; (10) written informed consent. Exclusions were: (1) the following histologies: malignant mesothelioma, chondrosarcoma, neuroblastoma, Ewing's sarcoma, embryonal rhabdomyosarcoma; (2) patient pregnant or breast feeding; (3) cardiac disease NYHA class II or greater; (4) uncontrolled infection; (5) radiotherapy in the last 6 weeks or to $>$35% of haemopoietic sites; (6) symptomatic brain metastases; (7) any other active malignant tumour apart from basal or squamous cell carcinoma of skin or cervical carcinoma *in situ*. All investigators were required to submit histology slides for central review according to the standard procedures of the Group.

2.2. Study design and drug administration

This was a randomised, multicentre study of previously untreated patients with adult STS. CAELYX® was administered as a 1 h i.v. infusion at 50 mg/m^2 every 4 weeks. Doxorubicin was given at a dose of 75 mg/m^2 as a 5 min i.v. bolus injection every 3 weeks. It was intended that patients would receive a total of six cycles in view of the possible cardiotoxicity of doxorubicin. The study was approved by the Research Ethics Committee of each participating institution. Patients

were given written information about the study, including detailed advice as to how to minimise skin toxicity from CAELYX®, and gave written informed consent.

Toxicity information was collected and graded according to Common Toxicity Criteria–National Cancer Institute of Canada (CTC–NCIC) criteria. Dose modifications for toxicity were allowed: for CAELYX® from 50 mg/m^2 down to 37.5 or 25 mg/m^2 and for doxorubicin from 75 mg/m^2 down to 60 or 45 mg/m^2, i.e. by one dose level or two dose levels in each case. A dose reduction by one dose level was allowed in the case of grade 4 neutropenia lasting for $\geqslant 7$ days, and by two dose levels if this was associated with febrile neutropenia and grade 4 thrombocytopenia.

Dose reductions were also allowed in the case of refractory gastrointestinal toxicity, including mucositis of grade $\geqslant 3$. In the case of skin toxicity (PPE) due to CAELYX®, the dose interval could also be increased. In the case of mild toxicity resolving to grade 1, treatment continued every 4 weeks; in the case of more severed toxicity, treatment was delayed for 1 week and if toxicity persisted for 2 weeks the dose was reduced by 25%. In the case of persisting grade 3 or 4 toxicity, after a 2 week delay patients were withdrawn from study.

Hypersensitivity reactions were known to occur with CAELYX® comprising flushing, shortness of breath, tightness in chest and throat. Instructions were given to stop the infusion, allow the problem to resolve and recommence treatment at 50% of the original infusion rate.

2.3. Response assessment

Patients were assessed for response before the start of treatment and after each two subsequent courses. Minimum tumour size criteria for measurability were applied as for all EORTC STBSG studies. Responses were assessed according to standard WHO criteria [11]. Response duration was measured from the start of treatment to the date of documented progression except in the case of complete response which was measured from the date of first documentation of complete response. Complete and partial responses had to be confirmed by repeat evaluation at least 4 weeks later. All objective responses were confirmed by two independent investigators according to the standard procedures of the Group.

2.4. Statistical considerations

The Simon two-stage testing procedure was used with the following parameters: P_0, the largest response probability implying that further investigation was not warranted, was set at 10%; P_1, the lowest response probability implying that further investigation was warranted, was set at 25%; α, the probability of recommending further study if the true response rate was $\leqslant P_0$, was set at 0.l; and β, the probability of rejecting further study if the true response rate was $\geqslant P_1$, was set at 0.1. The total sample size was to be 40 patients, with the possibility that the study could be closed with 27 patients evaluable for response if there were $\leqslant 2$ responses observed. Once 40 patients were evaluable for response, a second test was to be performed such that if $\leqslant 6$ responses were observed, the conclusion would be that further investigation was not justified, and if >6 responses were observed, further investigation was justified. Duration of response was calculated using the Kaplan–Meier method for all patients with a complete or partial response.

3. Results

3.1. Patients

The demographic details are shown in Table 1. Patients are well matched for age, performance status and prior therapy. In total, 95 patients were entered into the study (Fig. 1). Two patients randomised to doxorubicin did not receive treatment as part of the study. One was ineligible due to lack of regulatory approval in that country at the time, owing to an administrative oversight, and one refused treatment after randomisa-

Table 1
Demographic details

	CAELYX® ($N=50$)	Doxorubicin ($N=45$)
	n (%)	*n* (%)
Sex		
Male	26 (52)	20 (44)
Female	24 (48)	25 (56)
Median age (years) (range)	52 (19–80)	52 (27–77)
WHO performance status		
0	20 (40)	12 (27)
1	23 (46)	28 (62)
2	7 (14)	5 (11)
Previous surgery		
No	8 (16)	4 (9)
Yes — curative	31 (62)	27 (60)
Yes — palliative	8 (16)	11 (24)
Biopsy only	3 (6)	3 (7)
Previous radiotherapy		
No	36 (72)	31 (69)
Yes — excluding haematopoietic sites	11 (22)	13 (29)
Yes — including haematopoietic sites	3 (6)	1 (2)
Previous chemotherapy		
No	48 (96)	44 (98)
Yes — (neo)adjuvant	2 (4)	1 (2)

WHO, World Health Organization.

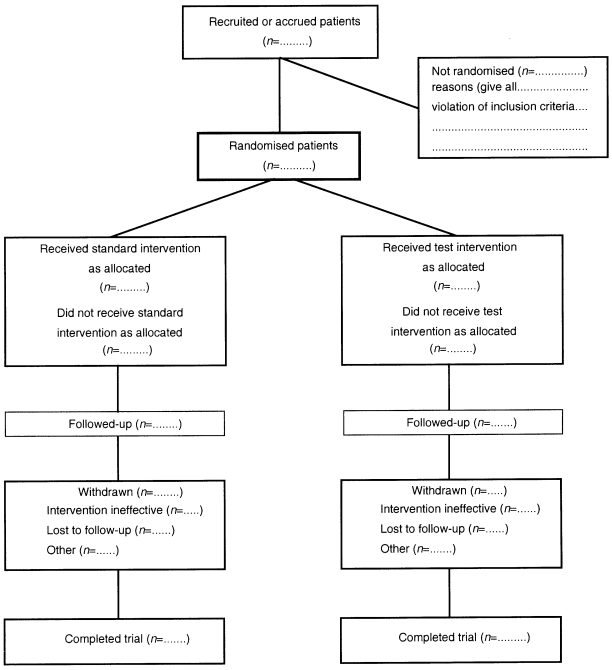

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Begg C, Cho M, Eastwood S, *et al*. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996; **276**: 637–639).

tion. The analysis has been conducted according to intention to treat.

The histological subtypes are given in Table 2 and the sites of primary disease in Table 3. There are no major differences between the two groups in the distribution of disease sites. There were slightly more patients with leiomyosarcoma and visceral intra-abdominal site in the CAELYX® arm and more liposarcomas in the doxorubicin arm. At the time the study commenced, it was not routine procedure to stratify according to disease site and gastrointestinal stromal tumour (GIST) was not universally distinguished from gastrointestinal leiomyosarcoma by local histopathologists. However, a careful analysis of the disease site suggests that 24% of patients receiving CAELYX® and 20% of those receiving doxorubicin had a GIST according to the designation of the site as visceral abdominal. In addition, there were a further three abdominal leiomyosarcomas in the CAELYX® arm and two in the doxorubicin arm. If these are included the total number of GIST cases was 15 (30%) and 11 (24%), respectively. Given the characteristically low response rate of this subtype, this would clearly have a major impact on the overall response rate observed. All sites of disease are shown in Table 4. It is of note that a significant number of patients had active disease at the primary site, predominantly those with visceral and retroperitoneal tumours. In keeping with this was the significant incidence of liver metastases: 13 (26%) in the CAELYX® arm, 11 (24%) in the doxorubicin arm.

The median total number of cycles administered was three for CAELYX® (range 1–8) and four for doxorubicin (range 0–8) which equates to an identical median duration of treatment of 84 days (Table 5). The relative median dose intensity was 99% (range 70–107) for CAELYX® and 98% (range 73–104) for doxorubicin. There was a similar percentage of treatment delay,

Table 3
Primary disease site

Localisation of the primary (all histologies)	CAELYX® ($N=50$)	Doxorubicin ($N=45$)	Overall ($N=95$)
	n (%)	*n* (%)	*n* (%)
Visceral intra-abdominal	12 (24)	9 (20)	21 (22)
Retroperitoneal	8 (16)	5 (11)	13 (14)
Lower limb and hip girdle	10 (20)	10 (22)	20 (21)
Upper limb and shoulder girdle	6 (12)	6 (13)	12 (13)
Uterus	7 (14)	5 (11)	12 (13)
Trunk	5 (10)	7 (16)	12 (13)
Neck	2 (4)	1 (2)	3 (3)
Breast	0 (0)	1 (2)	1 (1)
Face	0 (0)	1 (2)	1 (1)

Table 2
Histology

Histological subtype	CAELYX® ($N=50$)	Doxorubicin ($N=45$)	Overall ($N=95$)
	n (%)	*n* (%)	*n* (%)
Leiomyosarcoma	18 (36)	13 (29)	31 (33)
Miscellaneous sarcoma	8 (16)	5 (11)	13 (14)
Angiosarcoma	5 (10)	6 (13)	11 (12)
Synovial sarcoma	6 (12)	5 (11)	11 (12)
Unclassified sarcoma	6 (12)	3 (7)	9 (9)
Liposarcoma	1 (2)	7 (16)	8 (8)
Malignant fibrous histiocytoma	2 (4)	4 (9)	6 (6)
Neurogenic sarcoma	2 (4)	2 (4)	4 (4)
Fibrosarcoma	1 (2)		1 (1)
Rhabdomyosarcoma	1 (2)		1 (1)

Table 4
Sites of disease at times of treatment

Site	CAELYX® ($N=50$)	Doxorubicin ($N=45$)
	n (%)	*n* (%)
Primary	17 (34)	22 (49)
Lymph node	9 (18)	5 (11)
Lung	30 (60)	26 (58)
Liver	13 (26)	11 (24)
Skin	2 (4)	3 (7)
Other soft tissue (including visceral)	15 (30)	12 (27)
Bone	4 (8)	4 (9)
Brain	0 (0)	0 (0)
Ascites	0 (0)	1 (2)
Pleural effusion	1 (2)	3 (7)

Table 5
Treatment cycles

No. cycles	CAELYX® *n* (%)	Doxorubicin *n* (%)
0	0	2 (4)
1	3 (6)	4 (9)
2	19 (38)	11 (24)
3	9 (18)	5 (11)
4	7 (14)	6 (13)
5	3 (6)	0 (0)
6	7 (14)	14 (31)
7	1 (2)	2 (4)
8	1 (2)	1 (2)

but this was more likely to be due to non-haematological toxicity in the case of CAELYX®. Treatment was usually discontinued because of disease progression. Only 5 patients (10%) receiving CAELYX® and 6 (13%) receiving doxorubicin stopped treatment because of toxicity.

As expected, there were marked differences in the toxicity observed (Tables 6 and 7). Doxorubicin caused more myelosuppression, both neutrophils and platelets, and more febrile neutropenia. Alopecia was more severe with doxorubicin and skin toxicity with CAELYX®. However, mucositis, nausea and vomiting, and lethargy were similar in the two arms. Serious cardiotoxicity was not observed, but grade 1 and 2 impairment of ventricular function was significantly more common with doxorubicin (Fisher's Exact test $P=0.04$). Allergic reactions were rare and flu-like symptoms were not more frequent with CAELYX®.

Response data are shown in Table 8. The number of responses observed was lower than expected. There were five confirmed responses on CAELYX®, one complete and four partial; and four on doxorubicin, one complete and three partial, giving response rates of 10 and 9%,

Table 6
Haematological toxicity

CTC (NCIC) grade	0 *n* (%)	1 *n* (%)	2 *n* (%)	3 *n* (%)	4 *n* (%)
Leucopenia					
CAELYX®	27 (54)	15 (30)	7 (14)	1 (2)	0
Doxorubicin	2 (5)	5 (12)	11 (26)	20 (47)	5 (12)
Neutropenia					
CAELYX®	31 (62)	10 (20)	6 (12)	2 (4)	1 (2)
Doxorubicin	5 (12)	3 (7)	2 (5)	13 (30)	20 (47)
Thrombocytopenia					
CAELYX®	50 (100)	0	0	0	0
Doxorubicin	37 (86)	4 (9)	1 (2)	1 (2)	0
Haemoglobin					
CAELYX®	26 (52)	10 (20)	9 (18)	2 (4)	3 (6)
Doxorubicin	11 (26)	9 (21)	21 (49)	2 (5)	0

CTC, common toxicity criteria; NCIC, National Cancer Institute of Canada.

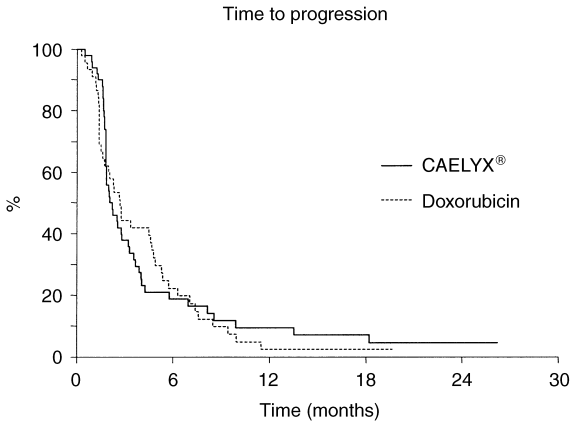

Fig. 2. Percentage probability of progression-free survival versus time.

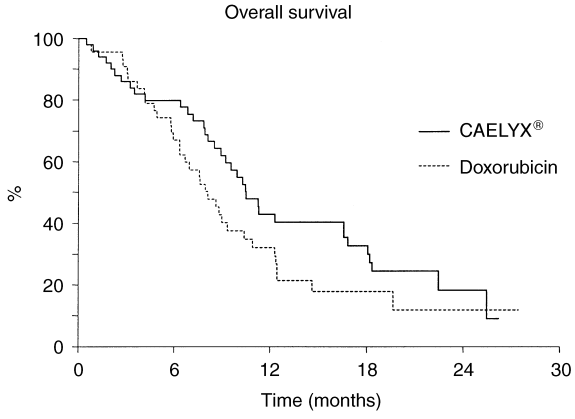

Fig. 3. Percentage probability of survival versus time.

respectively. If GIST cases were to be excluded for the purpose of response rates, these would increase to l4 and 12%, respectively. Median time to progression for all patients was 65 days for CAELYX® (95% confidence interval (CI) 55–98 days) and 82 days for doxorubicin (95% CI 52–143 days). The median estimate overall survival was 320 days for the CAELYX® arm (95% CI 272–505 days) and 246 days for doxorubicin (95% CI 193–316 days). Progression-free and overall survival curves are shown in Figs. 2 and 3. There were no significant differences between the two treatment arms.

4. Discussion

As expected, CAELYX® demonstrated antitumour activity in this population of patients with advanced adult STS, with reduced toxicity compared with standard i.v. bolus doxorubicin with the exception of skin toxicity, which was more severe. This is in keeping with reports from phase II trials in other tumour types [9,12]. The level of antitumour activity was similar in the two arms. Previously reported single arm phase II studies in

sarcoma have produced variable results, but indicated some activity in this disease [13,14].

In previously reported studies using doxorubicin in sarcomas, either as a single agent or in combination with other drugs such as ifosfamide, a response rate of $\geqslant 20\%$ has usually been observed [3,4,15,16]. One exception, a more recent trial, also by the EORTC STBSG, involved a comparison between doxorubicin, given as a standard i.v. bolus at 75 mg/m^2, and high-dose epirubicin at 150 mg/m^2, using two different schedules of administration. This reported a low response rate of 14%, which was not significantly different across the three arms of the study [17]. In this study, even if patients with GIST were to be excluded,

Table 7
Non-haematological toxicity

CTC (NCIC) grade		0 *n* (%)	1 *n* (%)	2 *n* (%)	3 *n* (%)	4 *n* (%)
Gastrointestinal						
Nausea	CAELYX®	17 (35)	18 (37)	14 (29)		
	Doxorubicin	13 (30)	14 (33)	15 (35)	1 (2)	
Vomiting	CAELYX®	33 (67)	11 (22)	5 (10)		
	Doxorubicin	26 (60)	9 (21)	7 (16)	1 (2)	
Diarrhoea	CAELYX®	41 (84)	7 (14)	1 (2)		
	Doxorubicin	32 (74)	5 (12)	5 (12)	1 (2)	
Stomatitis — oral	CAELYX®	22 (45)	10 (20)	15 (31)	2 (4)	
	Doxorubicin	21 (49)	8 (19)	12 (28)	2 (5)	
Anorexia	CAELYX®	43 (88)	3 (6)	2 (4)	1 (2)	
	Doxorubicin	29 (67)	8 (19)	4 (9)	2 (5)	
Infection						
Any infection	CAELYX®	36 (73)	5 (10)	6 (12)	2 (4)	
	Doxorubicin	32 (74)	2 (5)	6 (14)	3 (7)	
Febrile neutropenia	Caelyx	48 (98)			1 (2)	
	Doxorubicin	36 (84)			7 (16)	
Allergy						
Acute reaction	CAELYX®	47 (96)	1 (2)	1 (2)		
	Doxorubicin	42 (98)	1 (2)			
Skin						
Alopecia	CAELYX®	40 (82)	6 (12)	2 (4)	1 (2)	
	Doxorubicin	2 (5)	4 (9)	28 (65)	9 (21)	
Local toxicity	CAELYX®	47 (96)	2 (4)			
	Doxorubicin	42 (98)	1 (2)			
Palmar-plantar erythrodysesthesia	CAELYX®	24 (49)	4 (8)	11 (22)	9 (18)	1 (2)
	Doxorubicin	43 (100)				
Other	CAELYX®	34 (69)	6 (12)	6 (12)	3 (6)	
	Doxorubicin	38 (88)	4 (9)	1 (2)		
Pulmonary						
Cough	CAELYX®	43 (88)	3 (6)	1 (2)	2 (4)	
	Doxorubicin	33 (77)	7 (16)	3 (7)		
Shortness of breath	CAELYX®	41 (84)	3 (6)	3 (6)	1 (2)	1 (2)
	Doxorubicin	37 (86)	3 (7)	1 (2)	1 (2)	1 (2)
Other	CAELYX®	46 (94)	1 (2)		1 (2)	1 (2)
	Doxorubicin	39 (91)	1 (2)	2 (5)	1 (2)	
Ventricular function[a]	CAELYX®	50 (100)				
	Doxorubicin	39 (91)	3 (7)	1 (2)		
Flu-like symptoms						
Fever without infection	CAELYX®	39 (80)	6 (12)	4 (8)		
	Doxorubicin	34 (79)	5 (12)	4 (9)		
Lethargy	CAELYX®	31 (63)	5 (10)	10 (20)	3 (6)	
	Doxorubicin	22 (51)	12 (28)	8 (19)	1 (2)	
Myalgia	CAELYX®	45 (92)	2 (4)	2 (4)		
	Doxorubicin	41 (95)	1 (2)	1 (2)		
Other	CAELYX®	42 (86)	3 (6)	3 (6)	1 (2)	
	Doxorubicin	37 (86)	4 (9)	2 (5)		

[a] Statistically different incidence of cardiotoxicity, Fisher's Exact test, $P = 0.04$.

Table 8

Response	CAELYX® ($N=50$)	Doxorubicin ($N=45$)
	n (%)	*n* (%)
Complete response	1 (2)	1 (2)
Partial response	4 (8)	3 (7)
No change	16 (32)	18 (40)
Progressive disease	24 (48)	20 (44)
Early death due to malignant disease	4 (8)	1 (2)
Not assessable[a]	1 (2)	2 (4)
95% confidence interval	3.33–21.8	2.47–21.2

[a] 2 patients randomised to doxorubicin did not receive treatment in the trial: 1 was ineligible owing to the lack of regulatory approval and 1 refused treatment after randomisation.
One patient with CAELYX® discontinued treatment after the first cycle because of clinical disease progression.

the response rates were only 14% for CAELYX® and 12% for doxorubicin.

Why should response rates to doxorubicin vary and be appearing to fall? It is possible that the stringent response review procedures now in place in the STBSG have lowered reported response rates to some degree. However, it has not been our experience that >50% of responses fail to be confirmed by the independent assessors. The proportion of patients with GIST tumours appears to have been high, reducing the expected response rate. However, this was not dissimilar to certain other studies in which the response to doxorubicin was greater. It is notable that there were relatively few patients with sarcomas of the extremities.

The prognostic factors for response to chemotherapy have been studied in some detail by the EORTC STBSG [18]. Favourable factors for response were young age, high grade, absence of liver metastases and liposarcoma. These were different from the factors predicting long survival. The most common site of metastatic disease in this study was the lung, but a significant percentage of patients had liver metastases, an unfavourable factor for response. The median age was typical for STS. However, a number of elderly patients were treated, as allowed by the protocol.

It is possible that the perception of investigators and/or patients was that this study had a rather lower likelihood of toxicity, particularly in the CAELYX® arm, compared with certain recent studies performed by the group. This may have led to the selection of patients with relatively indolent disease and hence a lower likelihood of response. It is known that lymphoma case selection can largely determine response, an observation which led to the development of the International Prognostic Factors Index [19]. Perhaps in the future better stratification of patients with STS will be possible and it will be easier to explain the discrepancies in response between studies that are currently observed.

In conclusion, it appears that the sterically modified liposomal doxorubicin, CAELYX® (DOXIL®), has equivalent activity to standard doxorubicin in the treatment of advanced STS. The toxicity of the two drugs is markedly different, doxorubicin causing myelosuppression, alopecia and cardiotoxicity, whereas these problems are not seen with CAELYX®. However, with the dose and schedule used, skin toxicity from CAELYX® was troublesome in percentage of patients. Crucially, the lack of myelosuppression suggests that combinations of CAELYX® with myelosuppressive agents such as ifosfamide should be explored in the treatment of these difficult tumours.

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