PERGAMON

European Journal of Cancer 37 (2001) 2015–2022

European Journal of Cancer

www.ejconline.com

Phase II study of pegylated liposomal doxorubicin (Caelyx™) as induction chemotherapy for patients with squamous cell cancer of the head and neck

K.J. Harrington[a,b,*], C. Lewanski[c], A.D. Northcote[c], J. Whittaker[d], A.M. Peters[e], R.G. Vile[a,b], J.S.W. Stewart[c]

[a]*ICRF Laboratory of Molecular Therapy, Imperial College of Science, Technology and Medicine, Hammersmith Hospital, 150 Du Cane Road, London W12 0HS, UK*

[b]*Molecular Medicine Program, Guggenheim 1836, Mayo Clinic, 200 1st Street SW, Rochester, MN 55902, USA*

[c]*Department of Clinical Oncology, Charing Cross Hospital, Hammersmith Hospitals NHS Trust, Fulham Palace Road, London W6 8RF, UK*

[d]*ALZA Corporation, Mountain View, CA, USA*

[e]*Department of Imaging, Imperial College of Science, Technology and Medicine, Hammersmith Hospital, 150 Du Cane Road, London W12 0HS, UK*

Received 5 December 2000; received in revised form 22 May 2001; accepted 14 June 2001

Abstract

A phase II trial of pegylated liposomal doxorubicin (Caelyx™) as induction chemotherapy was conducted in 20 patients with treatment-naïve squamous cell cancer of the head and neck (SCCHN). 10 patients received two cycles of Caelyx™ (40 mg/m^2) every 3 weeks before starting radical radiotherapy (RT). Subsequently, consecutive groups of 3 patients received a third escalating dose of Caelyx™ (10, 15 and 20 mg/m^2) 3 days before RT. 9 of 18 (50%, 95% confidence intervals (CI): 26–74%) evaluable patients responded to Caelyx™, with 11 responses in 26 (42%, 95% CI: 24–62%) evaluable sites (three complete responses (12%), eight partial responses (31%)). There was no grade 3/4 haematological, mucosal or cardiac toxicity. Nausea and vomiting were minimal. There were no drug-related RT delays. Local RT-induced toxicity was not increased. Caelyx™ has significant activity against SCCHN and warrants further investigation in this disease. In view of its tumour targeting properties and activity at moderate doses, it may be useful in concomitant chemoradiotherapy strategies for SCCHN.

Keywords: Doxorubicin; Head and neck cancer; Pegylated liposome; Radiotherapy; Response; Toxicity

1. Introduction

The poor prognosis of patients with locally advanced squamous cell cancer of the head and neck (SCCHN) who are treated with surgery, radiotherapy (RT) or combinations of these treatments has prompted the search for more effective approaches incorporating cytotoxic chemotherapy into multimodality strategies [1,2]. Two recent overview analyses have demonstrated that the addition of chemotherapy to radical RT improves survival. Most benefit accrues from concomitant chemoradiotherapy (CCRT), with a survival advantage of 8–12% [3,4]. Published data support the activity of anthracycline-based chemotherapy in treating patients with head and neck cancer [5–8], although the majority of patients in those studies had locally recurrent or metastatic disease and had received prior therapy. Response rates of 12–13% have been reported for single agent epirubicin in patients with relapsed disease [7,8]. Doxorubicin has been incorporated in combination regimens, although the presence of other active agents has obscured the contribution of doxorubicin to the therapeutic effect [5,6].

It has been suggested that pegylated liposomes might enhance the therapeutic efficacy of cytotoxic agents in combination with RT [9]. Cytotoxic agents entrapped in pegylated liposomes have improved pharmacokinetics [10,11], increased tumour localisation [9–16], enhanced

* Corresponding author at affiliation b. Tel.: +507-538-0727l; fax: +507-266-4797.

E-mail address: harrington.kevin@mayo.edu (K.J. Harrington).

0959-8049/01/$ - see front matter
PII: S0959-8049(01)00216-7

therapeutic efficacy [9,17–21] and attenuated toxicity profiles [15,17,21] when compared with the corresponding unencapsulated agent in preclinical studies. We have recently demonstrated that radiolabelled pegylated liposomes localise to locally advanced head and neck tumours in patients [22] and that Caelyx™ is active against head and neck cancer xenograft tumours in nude mice, both as definitive therapy [21] and at lower doses in conjunction with RT [9]. In addition, pegylated liposomal doxorubicin (Caelyx™, ALZA Corporation, USA) has been subjected to a Phase I evaluation in patients with recurrent or metastatic SCCHN and a response rate of 33% was reported [23].

Therefore, as an extension of this work, we have conducted a trial of Caelyx™ in patients with SCCHN. For this initial study, it was decided to use induction, rather than concomitant, chemotherapy for two reasons. First, there were concerns about the risk of liposomal drug deposition in normal tissues exacerbating the toxicity of RT. Second, in our institution there is an interval of approximately 6 weeks between diagnosis and commencement of RT during which treatment planning occurs. This interval offers the opportunity to deliver two cycles of induction chemotherapy without delaying the start of radical RT. Therefore, it was decided that this study design represented a pragmatic means of achieving the following aims: (i) to assess the response of inoperable locally advanced treatment-naïve SCCHN to 2 cycles of Caelyx™ (40 mg/m^2 every 3 weeks) administered as induction treatment; (ii) to evaluate the ability to deliver a radical course of hyperfractionated RT after induction treatment with Caelyx™.

2. Patients and methods

2.1. Eligibility

An open, uncontrolled, non-randomised, single centre phase II trial was conducted in patients with locally advanced SCCHN. This study was approved by the Research Ethics Committee of the Hammersmith Hospitals NHS Trust. The inclusion criteria were: biopsy-proven, locally advanced, inoperable SCCHN; no prior therapy; at least one lesion measureable bidimensionally by physical or radiological examination; age 18–75 years; Karnofsky Performance Score (KPS) $\geqslant 60\%$; adequate bone marrow (absolute neutrophil count $\geqslant 2000\times10^6$ cells/l, platelet count $\geqslant 100\times10^9$ cells/l, hepatic (total bilirubin $\leqslant 20$ μg/l, serum transaminases $\leqslant$twice upper limit of normal) and renal (serum creatinine $< 125\%$ upper limit of normal) function; written informed consent. These exclusion criteria were applied: systemic metastatic disease, prior chemotherapy, RT or surgery (other than biopsy) to primary and/or neck disease; acute infection requiring systemic therapy; life expectancy <3 months; another primary tumour under treatment (except epithelial skin carcinoma). In view of the extensive data demonstrating that Caelyx™, even at high doses, is not associated with cardiotoxicity [24,25], normal left ventricular ejection fraction (LVEF) was not specified as an entry criterion, although it was measured as part of the assessment of toxicity.

2.2. Administration of Caelyx™

Caelyx™ (ALZA Corporation, Mountain View, CA, USA) was diluted in 250–500 ml 5% dextrose on the day of treatment and protected from the light. The drug was administered as a slow intravenous (i.v.) infusion over 1–2 h. Routine prophylactic anti-emetic medication was not used. In the first phase of the study, 10 patients received two cycles of 40 mg/m^2 every 3 weeks and were evaluable for response and toxicity of Caelyx™ and for the toxicity of radical RT commencing 3 weeks after the second cycle. When this phase of the study was completed, subsequent patients received a third cycle of Caelyx™ given 3 days before starting RT. Consecutive groups of 3 patients received escalating doses of Caelyx™ starting at 10 mg/m^2 and increasing through 15 mg/m^2 to 20 mg/m^2. Each cohort was monitored for evidence of increased acute radiation toxicity before proceeding to the next dose level.

2.3. Radiotherapy

For the first 10 patients, RT was commenced 21–25 days after the second dose of Caelyx™. For those patients who received a third dose of the drug, RT started 3 days after the third dose. Individualised supine immobilisation shells were made and treatment was planned on a Philips SLS-CT Simulator (Electa, Crawley, UK). Treatment consisted of twice-daily fractionated, split-course RT according to the schedule described by Wang and colleagues (1985) [26]. This schedule consists of two phases of dose-intense radiation delivery with a 10–12 day gap between the phases. The overall time of treatment with this regimen is 37–40 days which means that it is delivered more rapidly than conventionally fractionated radiation. At the time that this study was conducted, this fractionation regimen was being used as one of the four arms of the Radiation Therapy Oncology Group (RTOG) 9003 fractionation study and was the standard therapeutic protocol for locally advanced head and neck cancer in our institute. Recruitment to this study was completed before the results of the RTOG 9003 study were published, demonstrating that twice-daily split course treatment was inferior to hyperfractionated or concomitant boost fractionation regimens [27]. In phase I, the primary

tumour and loco-regional nodes received 38.4 Gy in 24 fractions over 2.5 weeks prescribed as a midplane dose using 6–8 MV photons treating each field twice daily with a minimum interfraction interval of 6 h. The elective nodal areas were also treated in phase I using a split anterior neck field with lead shielding to the midline and lung apices. The same RT dose was prescribed to this area as an applied dose. Phase I was followed by a 10–12 day gap in the treatment and then the patient proceeded to phase II treatment to a dose of 25.6 Gy in 16 fractions over 1.5 weeks. For the treatment of the primary tumour, this was prescribed as a midplane dose using 6–8 MV photons, treating each field twice daily with a minimum interfraction interval of 6 h. The spinal cord dose was limited to 38.4 Gy from the phase I treatment. If nodal disease overlying the spinal cord needed further treatment, posterior electron strips were used matched at the skin surface with the energy selected to avoid delivery of a dose exceeding radiotolerance to the spinal cord (usually 90–12 MeV electrons). In the presence of involved neck nodes, the low neck also received phase II radiation doses of 9.6–25.6 Gy depending on the site of the disease.

2.4. Evaluation of response

Formal response evaluation was carried out after two cycles of Caelyx™ and after radical RT by clinical and repeated radiological examination. All imaging was evaluated by a single radiologist using the World Health Organization (WHO) criteria for tumour response. In addition, changes in tumour volumes were calculated by reconstructing the tumour volume from computed tomography (CT) scans. CT images were digitised using a Sony DSC-F1 camera mounted on a standard jig and enlarged to life size using Adobe Photoshop Software Program 5.0 (Adobe Systems Inc., San Jose, CA, USA). The tumour area for each CT image was measured using the pixel count facility and tumour volume (TV) was calculated from: $TV = \Sigma AD$, where A is tumour area from the pixel count and D is distance between images.

2.5. Toxicity assessment

Haematological and non-haematological toxicities were assessed during the initial two cycles of Caelyx™ and during the RT. Cardiac function was assessed on entry by 12-lead electrocardiogram (ECG) and nuclear medicine MUGA scan. A repeat ECG and MUGA scan was performed after cycle 2 and another ECG was performed 6 weeks after RT. Stomatitis/mucositis, palmar-plantar erythrodysaesthesia (PPE) and myelosuppression were recorded weekly using the National Cancer Institute (NCI) Common Toxicity Criteria. 6 patients required insertion of a naso-gastric tube or percutaneous endoscopic gastrostomy to maintain enteral feeding because of the presence (or risk) of aspiration. In these cases, separate assessments of treatment-related mucosal toxicity were made.

3. Results

3.1. Patient demographics

20 patients (17 males, 3 females) entered the study. The median age was 63 years (range: 46–77 years) and the median KPS was 90% (range 60–100%). The distribution of tumour sites was as follows: oral cavity—1 patient; oropharynx—8 patients, larynx (supraglottic)—5 patients; hypopharynx—6 patients. The TNM stages were distributed as follows: T1—2 patients; T3—9 patients; T4—9 patients; N0—10 patients; N1—2 patients; N2—6 patients; N3—2 patients.

3.2. Response data

18 patients were fully evaluable for response and toxicity of the initial two cycles of Caelyx™. There were 26 sites of disease in the 18 evaluable patients (16 primary tumour sites and 10 nodal metastases). In 2 patients, the primary pyriform fossa tumour was inevaluable, but both had N3 neck disease which was readily evaluable. Individual patient response data are presented in Table 1 and summarised in Table 2. Overall, 9 of 18 (50%, 95% confidence intervals (CI): 26–74%) patients showed an objective response to the initial two cycles of Caelyx™ in the primary site and/or the nodal metastases. In total, there were 11 responses in 26 (42%, 95% CI: 24–62%) sites. There was evidence of a differential response according to the site of disease with nine of 16 (56%) primary sites, but only two of 10 (20%) nodal metastases, responding (Table 2).

The data relating to the assessment of tumour volume in response to treatment are presented in Figs. 1 and 2. The measured tumour volumes were in accord with the overall evaluation of response (as would be expected because CT scans were used as a primary means of classifying the response to treatment). However, the absolute measures of tumour volume presented some interesting findings. For the lesions that were classified as showing a PR, the mean change in tumour volumes ($\pm$S.D.) were $-66.7 \pm 16.2\%$ and $-64.4 \pm 14.6\%$ for the primary tumour and lymph node metastases, respectively. For the lesions that were classified as showing no response, the mean change in tumour volumes ($\pm$S.D.) were $-18.0 \pm 22.5\%$ and $+7.8 \pm 18.5\%$ for the primary tumour and lymph node metastases, respectively. Indeed, of the five primary tumour sites that were classified as no response by standard criteria, four showed a reduction in measured tumour volume. In contrast, two

Table 1
Details of patients treated with Caelyx™. Individual patient response data are provided for both induction Caelyx™ treatment and RT

No.	Age (years)	Sex	Tumour site	Stage	Caelyx™ response	RT response	Status
301	74	M	HP (pyriform fossa)	T4N1M0	PR—primary	CR—primary	PD—16 months, Died —18 months
					PR—node	CR—node	
302	53	M	OP (tongue base)	T4N2aM0	CR—primary	CR—primary	Radical neck dissection post-RT, residual disease
					NR—node	PR—node	PD—12 months, Died—14 months
303	71	M	HP (pyriform fossa)	T1N3M0	NE—primary	NE—primary	Radical neck dissection post-RT, pathological CR
					PD—node	CR node	NSR—34 months
304	69	F	OP (soft palate)	T4N2aM0	PR —primary	CR—primary	Palatal fistula post-treatment. Palatoplasty at 8 months.
					PR—node	CR—node	NSR—24 months
							Diagnosis of NSCLC at 14 months—treated with palliative RT
305	77	M	Larynx (supraglottis)	T4N0M0	NE	NE	Died cycle 1, week 3 (aspiration pneumonia at post mortem)
306	59	M	HP (pyriform fossa)	T1N3M0	NE—primary	NE—primary	Residual neck disease inoperable because fixed to skull base
					NR—node	PR—node	PD—6 months, Died—10 months
307	54	M	OP (tonsil/soft palate)	T4N2aM0	NR—primary	CR—primary	PD- 6 months
					PD—node	CR—node	Died—12 months
308	66	M	Larynx (supraglottis)	T3N0M0	PR—primary	CR—primary	NSR—30 months
309	73	M	HP (post-cricoid)	T3N0M0	NR—primary	CR—primary	NSR—30 months
310	63	M	Larynx (supraglottis)	T3N0M0	NE	NE	Died cycle 2, week 2 (aspiration pneumonia at post mortem)
311	63	F	OP (tonsil)	T3N2bM0	PR—primary	PR—primary	RT stopped at 48 Gy due to diagnosis of second cancer
					NR—node	PR—node	Died of stage IV ovarian cancer metastatic to liver—4 months
312	64	F	OC (floor of mouth)	T4N0M0	PR—primary	CR—primary	NSR—20 months
313	50	M	OP (tongue base)	T3N2bM0	NR—primary	PR—primary	RT stopped at 22.4 Gy due to diagnosis of second cancer
						PR—node	Died of oesophageal cancer metastatic to liver—6 months
314	58	M	OP (tongue base)	T4N2cM0	PD—primary	PD—primary	RT stopped at 38.4 Gy due to PD
					PD—node	PD—node	Died—9 months
315	47	M	Larynx (supraglottis)	T3N1M0	NR—primary	CR—primary	PD 19 months
					NR—node	PR—node	Alive with disease—28 months
316	46	M	OP (retromolar trigone)	T3N0M0	CR—primary	CR—primary	NSR—24 months
317	65	M	HP (post-cricoid)	T4N0M0	PR—primary	CR—primary	PD—6 months
							Died—11 months
318	56	M	OP (soft palate)	T3N0M0	CR—primary	CR—primary	NSR—22 months
319	72	M	Larynx (supraglottis)	T3N0M0	PD—primary	CR—primary	PD—3 months
							Died—9 months
320	48	M	HP (post-cricoid)	T4N0M0	NR—primary	NE —primary	Withdrew from study at 30.4 Gy
							Died—7 months

CR, complete response; HP, hypopharynx; NE, not evaluable; NR, non-response; NSCLC, non-small cell lung cancer; NSR, no sign of recurrence; OC, oral cavity; OP, oropharynx; PD, progressive disease; PR, partial response; M, male; F, female.

of four non-responding lymph nodes showed a reduction in volume (−4.4% and −11.6%, respectively). These data again suggest that the primary tumour site was more responsive to treatment than metastatic lymph node disease.

18 (90%) patients commenced radical RT, 14 of whom completed the treatment. Four patients stopped RT early: 2 patients were found to have liver metastases from synchronous primary tumours during RT; 1 patient had progressive disease during chemotherapy and RT; 1 patient withdrew during RT despite the fact that he was tolerating treatment well. When available, response and toxicity data from these 4 patients have been included in the final analysis. Therefore, of the 26 sites of disease in the 18 patients commencing RT, only 25 sites were evaluable in 17 patients at the end of RT (including those patients who did not receive a radical radiation dose). The individual patient response data to RT are presented in Table 1 and summarised in Table 3. Overall, 16 of 17 (94%) patients achieved an objective response to RT in the primary site and/or the nodal metastases. In total, there were 23 responses in the 25

Table 2
Response of primary tumour and neck nodal metastases to 2 cycles of Caelyx™

Response	Primary tumour ($n=16$)[a]	Nodal metastases ($n=10$)[b]
CR	3/16 (19%)	0/10 (0%)
PR	6/16 (38%)	2/10 (20%)
NR	5/16 (31%)	5/10 (50%)
PD	2/16 (13%)	3/10 (30%)

CR, complete response; PR, partial response; NR, non-response; PD, progressive disease.

[a] 4 patients not evaluable: 2 patients died before assessable for response, 2 patients with T1 pyriform fossa tumours.

[b] 10 patients with N0 neck stage.

Table 3
Response of primary tumour and neck nodal metastases to RT following Caelyx™

Response	Primary tumour ($n=15$)[a]	Nodal metastases ($n=10$)[b]
CR	12/15(80%)	4/10 (40%)
PR	2/15 (13%)	5/10 (50%)
NR	0/15 (0%)	0/10 (0%)
PD	1/15 (7%)	1/10 (10%)

CR, complete response; PR, partial response; NR, non-response; PD, progressive disease.

[a] 5 patients not evaluable: 2 patients died before assessable for response; 2 patients with T1 pyriform fossa tumours; 1 patient withdrew from study.

[b] 410 patients with N0 neck stage.

(92%) sites. There was no evidence of a differential response according to disease site with 14 of 15 (93%) primary sites and 9 of 10 (90%) nodal metastases, responding (Table 3).

After a median follow-up period of 17 months, 12 (60%) patients have died, 7 (35%) patients are free of recurrence of SCCHN and 1 (5%) patient is alive with recurrent disease. The median overall survival was 13 (range: 1–34 months) and the median progression-free survival was 12 months (range: 1–34 months). The causes of death were loco-regional recurrence (8 patients), synchronous primary cancers (2 patients) and aspiration pneumonia (2 patients).

3.3. Toxicity evaluation

20 patients received 39 cycles of 40 mg/m^2 Caelyx™, all of which were evaluable for toxicity. Nine cycles of treatment were administered to 9 patients according to the dose escalation protocol 3 days before the start of RT. 2 patients with large supraglottic tumours died of aspiration pneumonia during the study. Neither patient was neutropenic following chemotherapy. The occurrence of pneumonia was felt to be due to aspiration at

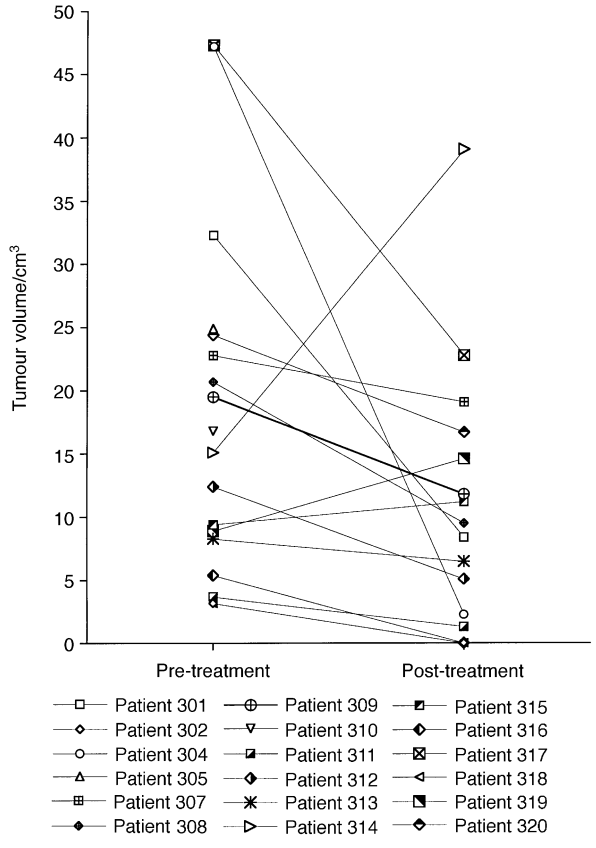

Fig. 1. Tumour volumes of primary squamous cell cancer o the head and neck (SCCHNs) in response to two cycles of Caelyx™. Patients 305 and 310 did not have post-chemotherapy response evaluation. The primary tumour was not assessable in patients 303 and 306.

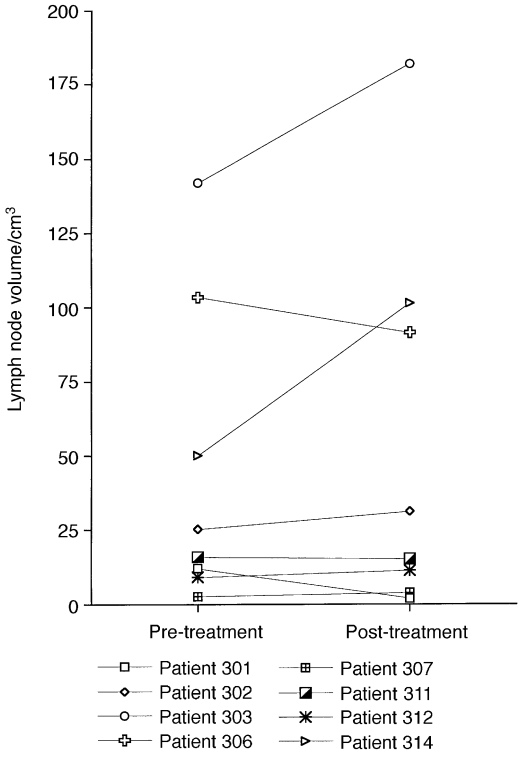

Fig. 2. Lymph node volumes in response to two cycles of Caelyx™ in 8 patients with assessable nodal metastases.

post mortem examination and unrelated to the administration of the study drug.

3.3.1. Acute infusion reaction

One cycle of treatment (3%) was associated with an initial infusion reaction (flushing, chest tightness, shortness of breath, abdominal and back pain) which settled within 5 min of discontinuing the infusion. The infusion was restarted slowly and completed without further symptoms. Subsequently, this patient received cycles 2 and 3 without incident.

3.3.2. Gastro-intestinal toxicity

None of the patients suffered nausea, vomiting or diarrhoea following treatment.

3.3.3. Haematological toxicity

The haematological toxicity grades for each patient are presented in Table 4. Only four cycles of chemotherapy in 3 patients (4/39, 10%) were complicated by leucopenia. Neutropenia occurred in three cycles in 2 patients (3/39, 8%) (grade 1—two cycles, grade 2—one cycle). The other episode of leucopenia was a grade 1 lymphopenia. Grade 1 thrombocytopenia occurred in two cycles in 1 patient. No patient required admission for treatment of neutropenic sepsis or thrombocytopenia. 13 (65%) patients had haemoglobin levels below the lower limit of the normal range (all grade 1 (>100 g/l)) before receiving chemotherapy. During chemotherapy, 17 patients had abnormal haemoglobin levels in cycles 1 and 2. There was only one episode of grade 2 anaemia with all other haemoglobin values >100 g/l. During the study, 14 patients received 21 autologous blood transfusions (52 units). Ten of these blood transfusions (26 units) were administered to 6 patients during the first two cycles of Caelyx™. Eleven blood transfusions (26 units) were administered before or during RT in keeping with a departmental policy on the avoidance of anaemia during radical RT in patients with SCCHN.

3.3.4. Mucocutaneous toxicity

The toxicity grades for PPE and mucositis for each patient are presented in Table 4. One patient (5%) experienced grade 1 alopecia. PPE affected 2 of 20 patients (10%) during cycle 1 and 9 of 18 patients (50%) in cycle 2. The grades of PPE documented in cycle 2 were appreciably higher than in cycle 1. PPE was not confined to the hands and feet, also occurring in the axillae (1 patient), trunk (1 patient), perineum (1 patient), pinna (1 patient) and at venepuncture sites (2 patients). No patient had PPE involving the skin of the face or neck. Stomatitis/mucositis affected 3 of 20

Table 4
Toxicity grades for palmar-plantar erythrodysaesthesia (PPE), mucositis (Muc) and haematological toxicity (Haem) for induction chemotherapy and subsequent radical radiotherapy

	PLED cycle 1			PLED cycle 2			RT week 1			RT week 2			RT week 3			RT week 4			RT week 5			RT week 6		
No.	PPE	Muc	Haem	PPE	Muc	Haem	PPE	Muc	Haem	PPE	Muc	Haem	PPE	Muc	Haem	PPE	Muc	Haem	PPE	Muc	Haem	PPE	Muc	Haem
301	0	0	1[a]	0	0	1[a]	0	0	1[a]	0	1	1[a]	0	2	1[a]	0	3	1[a,b]	0	2	1[a,b]	0	1	1[a]
302	0	1	1[a]	3	1	1[a]	1	2	1[a]	0	3	1[a]	0	2	1[a]	0	3	1[a]	0	2	1[a]	0	1	1[a]
303	0	0	1[a,b]	0	0	1[a]	0	0	1[a]	0	2	1[a]	0	3	1[a]	0	4	0	0	4	1[a]	0	4	1[a]
304	0	1	2[a]	0	2	1	0	0	1[a]	0	0	1[a]	0	2	1[a]	0	3	1[a]	0	2	1[a]	N/A	N/A	N/A
305	0	0	1[a]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
306	1	0	1[a]	2	0	1[a]	0	0	1[a]	0	1	1[a]	0	2	2[a]	0	3	2[a]	0	3	1[a]	N/A	N/A	N/A
307	0	0	0	0	0	0	0	0	0	0	2	0	0	3	1[a]	0	2	0	0	2	0	N/A	N/A	N/A
308	0	0	1[a]	0	0	1[a]	0	0	0	0	0	0	0	1	1[a]	0	2	0	0	2	1[a]	0	1	1[a]
309	0	0	1[a,b,c]	2	0	1[a,c]	2	0	1[a]	1	0	0	0	3	1[a]	0	2	1[a]	0	2	0	N/A	N/A	N/A
310	0	0	1[a]	0	0	0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
311	0	0	1[a]	2	0	1[a]	2	0	1[a]	1	2	1[a]	0	2	1[a]	0	3	1[a]	–	–	–	–	–	–
312	0	0	1[a]	0	0	1[a]	1	0	0	1	0	0	0	3	0	0	3	1[a]	0	3	1[a]	0	2	1[a]
313	0	1	1[a]	0	0	1[a]	0	0	1[a]	0	0	1[a]	–	–	–	–	–	–	–	–	–	–	–	–
314	0	0	1[a]	1	0	1[a]	0	0	0	0	2	1[a]	0	3	1[a]	0	3	1[a]	–	–	–	–	–	–
315	0	0	0	0	0	1[a]	0	0	1[a]	0	0	1[a]	0	2	1[a]	0	3	1[a]	0	3	1[a]	0	1	1[a]
316	0	0	1[a]	2	1	1[a]	0	2	1[a]	0	3	1[a]	0	3	0	0	3	0	0	2	1[a]	0	3	1[a]
317	0	0	1[a,b]	0	0	1[a,b]	0	0	0	0	0	0	0	1	1[a]	0	3	1[a]	0	3	0	0	3	1[a]
318	0	0	1[a]	2	1	1[a]	2	1	1[a]	1	2	0	1	3	0	0	3	0	0	2	1[a]	0	2	1[a]
319	0	0	0	1	0	0	2	0	0	3	0	0	3	2	0	0	2	0	0	4	0	0	3	0
320	1	0	1[a]	2	0	1[a]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

RT, radiotherapy; PLED, pegylated liposomal doxorubicin.

Patients 305 and 310 died of aspiration pneumonia during induction chemotherapy. Patients 311, 313, 314 and 320 did not complete the full course of radical radiotherapy.

[a] Haematological toxicity grade relating to Hb.

[b] Haematological toxicity grade relating to leukopenia.

[c] Haematological toxicity grade relating to thrombocytopenia.

patients (15%) in cycle 1 and 4 of 18 patients (22%) in cycle 2. Higher grades of mucositis were documented during cycle 2. There were no delays to the start of radical RT due to cutaneous or mucosal toxicity in the proposed radiation fields. Furthermore, it was possible to deliver the planned course of RT in all patients (apart from those patients in whom treatment was discontinued early for other reasons) without increased acute mucocutaneous toxicity or unscheduled treatment delays.

3.3.5. Cardiac toxicity

One patient had an LVEF below the lower limit of the normal range (34%) on entry. This value remained unchanged (35%) after two cycles of Caelyx™. No patient developed clinical symptoms (dyspnoea, orthopnoea, oedema, chest pain or palpitations) of cardiac dysfunction. The median LVEF was 58% (range: 34–78%) on entry to the study (normal >36%). For those patients who received two cycles of Caelyx™ and underwent a second MUGA scan, the median LVEF was 45% (range: 35–69%). The data for pre- and post-treatment LVEF were compared using the paired sample *t* test and were found not to be statistically significantly different ($P > 0.1$).

4. Discussion

The overall response rate of 42% (by tumour site) to two cycles of Caelyx™ (40 mg/m^2) as induction chemotherapy demonstrates that this agent possesses significant activity against treatment-naïve SCCHN. We are unaware of any comparable data for the use of unencapsulated doxorubicin as induction chemotherapy. Although this high response rate to Caelyx™ may, in part, be due to the fact that these patients had received no prior therapy, it is unlikely that this factor fully accounts for the impressive response rate. Rather, it is interesting to hypothesise that the alteration in the pharmacokinetics and biodistribution of doxorubicin resulting from the liposomal encapsulation explains the response to treatment, in an analogous fashion to the superior response seen with Caelyx™ compared with unencapsulated doxorubicin in the treatment of AIDS-related Kaposi's sarcoma (KS) [28,29]. This premise is supported by the observation of significant tumour targeting of radiolabelled pegylated liposomes in patients with SCCHN [22,30].

The explanation for the differential response pattern between the primary tumour and the nodal metastases is unclear. Nodal metastases often contain necrotic areas consistent with a poor blood supply and this factor has been shown to decrease liposome deposition in a tumour xenograft model [31]. In addition, large primary mucosal SCCHN often have associated inflammation and/or infection which have been shown to increase liposome deposition [32,33].

The fact that patients treated with two cycles of Caelyx™ followed by radical RT completed their treatment without unscheduled treatment breaks or excessive acute normal tissue toxicity suggests that cumulative deposition and/or release of liposome encapsulated drugs in normal tissues did not occur during induction chemotherapy. This lack of excessive radiation-induced normal tissue toxicity is an important observation. Therefore, administration of pegylated liposomes a number of days before RT may allow for optimal tumour localisation and normal tissue clearance, thus enhancing the therapeutic ratio. It was this supposition that lay behind the second phase of the study in which patients received a third dose of the Caelyx™ 3 days before the start of RT. It was decided to start this part of the study by administering a relatively low dose of 10 mg/m^2 and escalating the dose by 5 mg/m^2 through successive cohorts of three patients up to a dose of 20 mg/m^2.

In summary, Caelyx™ was shown to exert significant single agent activity against SCCHN and is certainly worthy of further investigation in this setting. However, it must be borne in mind that this was a relatively small study and the results should be viewed as hypothesis generating. Attempts to define the optimal dose and scheduling of Caelyx™ administration, including the value of abbreviated schedules aiming to achieve increased tumour concentrations of the agent before the start of RT should form the basis of future studies. In addition, evaluation of CCRT with pegylated liposomal agents during conventional and altered fractionation regimens may provide a means of optimising the benefits of this strategy.

Acknowledgements

STEALTH® liposomes are a registered trademark of ALZA Corporation, Mountain View, CA, USA. Supplies of Caelyx™ for this study were provided by ALZA Corporation.

References

1. Tannock IF. Treatment of cancer with radiation and drugs. *J Clin Oncol* 1996, **14**, 3156–3174.
2. Jeremic B, Shibamoto Y, Stanisavljevic B, *et al.* Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. *Radiother Oncol* 1997, **43**, 29–37.
3. Munro AJ. An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cancer. *Br J Cancer* 1995, **71**, 83–91.

4. Pignon JP, Bourhis J, Domengé C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. *Lancet* 2000, **355**, 949–955.
5. Creagan ET, Fleming TR, Edmonson JH, *et al*. Cyclophosphamide, adriamycin, and cis-diamminedichloroplatinum (II) in the treatment of patients with advanced head and neck cancer. *Cancer* 1981, **47**, 240–244.
6. Creagan ET, Chang M, Long HJ, *et al*. A phase II clinical trial of the combination mitomycin C, adriamycin, and cis-diamminedichloroplatinum in patients with advanced upper aerodigestive cancer. *Head Neck Surg* 1986, **8**, 153–158.
7. Martoni A, Giovannini M, Tomasi L. A phase II clinical trial of 4′-epi-doxorubicin in advanced solid tumors. *Cancer Chemother Pharmacol* 1984, **12**, 179–182.
8. Magee MJ, Howard J, Bosl GJ, *et al*. Phase II trial of 4′-epi-doxorubicin in advanced carcinoma of head and neck origin. *Cancer Treat Rep* 1985, **69**, 125–126.
9. Harrington KJ, Rowlinson-Busza G, Syrigos KN, *et al*. Pegylated liposome encapsulated doxorubicin and cisplatin enhance the effect of radiotherapy in a tumor xenograft model. *Clin Cancer Res* 2000, **6**, 4939–4949.
10. Gabizon A, Catane R, Uziely B, *et al*. Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polethylene-glycol coated liposomes. *Cancer Res* 1994, **54**, 987–992.
11. Klibanov AL, Maruyama K, Torchilin VP, *et al*. Amphipathic polyethyleneglycols effectively prolong the circulation times of liposomes. *FEBS Lett* 1990, **68**, 235–237.
12. Huang SK, Mayhew E, Gilani S, *et al*. Pharmacokinetics and therapeutics of sterically stabilised liposomes in mice bearing C-26 colon carcinoma. *Cancer Res* 1992, **52**, 6774–6781.
13. Huang SK, Lee K-D, Hong K, *et al*. Microscopic localisation of sterically stabilised liposomes in colon carcinoma-bearing mice. *Cancer Res* 1992, **52**, 5135–5143.
14. Huang SK, Martin FJ, Jay G, *et al*. Extravasation and transcytosis of liposomes in Kaposi's sarcoma-like dermal lesions of transgenic mice bearing the HIV *tat* gene. *Am J Pathol* 1993, **143**, 1–14.
15. Siegal T, Horowitz A, Gabizon A. Doxorubicin encapsulated in sterically stabilised liposomes for the treatment of a brain tumor model: biodistribution and therapeutic efficacy. *J Neurosurg* 1995, **83**, 1029–1037.
16. Vaage J, Barbera-Guillem E, Abra R, *et al*. Tissue distribution and therapeutic effect of intravenous free or encapsulated liposomal doxorubicin on human prostate carcinoma xenografts. *Cancer* 1994, **73**, 1478–1484.
17. Cabanes A, Tzemach D, Goren D, *et al*. Comparative study of the anti-tumor activity of free doxorubicin and polyethylene glycol-coated liposomal doxorubicin in a mouse lymphoma model. *Clin Cancer Res* 1998, **4**, 499–505.
18. Mayhew EG, Lasic D, Babbar S, *et al*. Pharmacokinetics and antitumor activity of epirubicin encapsulated in long-circulating liposomes incorporating a polyethylene glycol-derivatized phospholipid. *Int J Cancer* 1992, **51**, 302–309.
19. Vaage J, Donovan D, Mayhew E, *et al*. Therapy of mouse mammary carcinomas with vincristine and doxorubicin encapsulated in sterically stabilised liposomes. *Int J Cancer* 1993, **54**, 959–964.
20. Vaage J, Donovan D, Uster P, *et al*. Tumor uptake of doxorubicin in polyethylene glycol-coated liposomes and therapeutic effect against a xenografted human pancreatic carcinoma. *Br J Cancer* 1997, **75**, 482–486.
21. Harrington KJ, Rowlinson-Busza G, Uster PS, Stewart JSW. Pegylated liposome encapsulated doxorubicin and cisplatin in the treatment of head and neck xenograft tumors. *Cancer Chemother Pharmacol* 2000, **46**, 10–18.
22. Harrington KJ, Mohammadtaghi S, Uster PS, *et al*. Effective targeting of solid tumours in patients with locally advanced cancers by radiolabelled pegylated liposomes. *Clin Cancer Res* 2001, **7**, 243–254.
23. Caponigro F, Comella P, Budillon A, *et al*. Phase I study of Caelyx (doxorubicin HCL, pegylated liposomal) in recurrent or metastatic head and neck cancer. *Ann Oncol* 2000, **11**, 339–342.
24. Berry G, Billingham M, Alderman E, *et al*. The use of cardiac biopsy to demonstrate reduced cardiotoxicity in AIDS Kaposi's sarcoma patients treated with pegylated liposomal doxorubicin. *Ann Oncol* 1998, **9**, 711–716.
25. Safra T, Muggia F, Jeffers S, *et al*. Pegylated liposomal doxorubicin (doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m^2. *Ann Oncol* 2000, **11**, 1029–1033.
26. Wang CC, Blitzer PH, Suit HD. Twice-a-day radiation therapy for cancer of the head and neck. *Cancer* 1985, **55**, 2100–2104.
27. Fu KK, Pajak TF, Trotti A, *et al*. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000, **48**, 7–16.
28. Stewart JSW, Jablonowski H, Goebel F-D, *et al*. Randomised comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. *J Clin Oncol* 1998, **16**, 683–691.
29. Northfelt DW, Dezube B, Thommes JA, *et al*. Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomised phase III clinical trial. *J Clin Oncol* 1998, **16**, 2445–2451.
30. Koukourakis MI, Koukouraki S, Giatromanolaki A, *et al*. Liposomal doxorubicin and conventionally fractionated radiotherapy in the treatment of locally advanced non-small-cell lung cancer and head and neck cancer. *J Clin Oncol* 1999, **17**, 3512–3521.
31. Harrington KJ, Rowlinson-Busza G, Syrigos KN, *et al*. Influence of tumour size on uptake of ^{111}In-DTPA-labelled pegylated liposomes in a human tumour xenograft model. *Br J Cancer* 2000, **83**, 684–688.
32. Boerman OC, Storm G, Oyen WJG, *et al*. Sterically stabilised liposomes labeled with Indium-111 to image focal infection. *J Nucl Med* 1995, **36**, 1639–1644.
33. Oyen WJG, Boerman OC, Storm G, *et al*. Labelled Stealth® liposomes in experimental infection: an alternative to leukocyte scintigraphy? *Nucl Med Communic* 1996, **17**, 742–748.