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Locoregional effects of pegylated liposomal doxorubicin (Caelyx®) in irradiated area: a phase I–II study in patients with recurrent squamous cell carcinoma of the head and neck ☆

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Abstract

Aim of this study was to determine the antitumour activity and toxicity of pegylated liposomal doxorubicin (Caelyx®) in pretreated patients with locally recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). Caelyx was administrated as 1 h infusion every 3 weeks at doses of 35 mg/m^2 (group A) and then subsequently given at 45 mg/m^2 (group B). 26 patients received a total of 87 cycles. The median number of cycles was 3 (range 1–7). Four out of 24 evaluable patients (17%, 95% confidence interval (CI) 0.5–32%) showed significant evidence of antitumour activity, with tumour necrosis being observed in 2 patients. Grade 3–4 neutropenia was observed in only 2 patients. There were no grade 3–4 mucosal, skin, digestive, cardiac or hepatic toxicities. Caelyx has activity against locally recurrent SCCHN and is well tolerated up to 45 mg/m^2, but a careful utilisation of this drug is required for tumours relapsing in irradiated areas.

Keywords: Doxil; Head and neck cancer; Pegylated liposome; Response; Toxicity

1. Introduction

The prognosis of patients with recurrent squamous cell cancer of the head and neck (SCCHN) previously treated via locoregional modalities and/or chemotherapy remains disappointing and warrants new approaches including non-cross resistant molecules or improved galenic formulation of cytotoxic agents [1,2].

During the last two decades, anthracyclines have shown activity in treating patients with advanced or recurrent head and neck cancer, yielding response rates ranging from 18% to 44% [3–8]. However, considering haematological toxicity and the underlying concomitant cardiovascular comorbidities associated with tobacco consumption, the use of standard anthracylines has been progressively discouraged in patients with SCCHN.

Pegylated liposomes are stable and long-circulating drug carriers that have been proposed to improve the pharmacokinetic and intratumour delivery of doxorubicin [9,10] when compared with non-liposomal doxorubicin [11,12]. Clinical studies have reported low grade 3–4 haematological, mucosal or cardiac toxicities [13,14] and a particular pattern of mucositis and skin toxicity similar to that reported with protracted infusions of doxorubicin.

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It is proposed that such preparations result in a slow release of the drug in the intravascular compartment and/or its in situ release in mucous membrane and skin [15]. Caelyx is active against SCCHN xenografts [16] and has shown antitumour effects in patients with recurrent [17] and untreated locally advanced SCCHN [18].

This study aimed to determine the antitumour effects and the safety profile of Caelyx in patients with recurrent SCCHN using two consecutive groups of patients treated with doses of 35 and 45 mg/m^2, every 3 weeks.

2. Patients and methods

2.1. Patient population

This singlecentre phase I–II trial was conducted in patients with histologically-proven, locally recurrent or metastatic measurable computed tomography (CT) scan or magnetic resonance imaging (MRI) SCCHN. Other inclusion criteria were: at least 3 weeks interval from last prior chemotherapy regimen, age between 18 and 75 years, World Health Organisation (WHO) performance status 0–2 with a life expectancy of more than three months; normal left ventricular ejection fraction (LVEF) >70% calculated by cardiac ultrasound, adequate bone marrow function with an absolute neutrophil count $\geqslant 1500 \times 10^6$ cells/l, platelet count $\geqslant 100 \times 10^9$ cells/l, hemoglobin $\geqslant 80$ g/l, adequate hepatic function, detected by alkaline phosphatases and serum transaminases less than three times the upper limit of normal; serum creatinine less than two times the upper limit of normal; written informed consent, fulfilling all instructional and national guidelines.

Main exclusion criteria included history of cardiopathy with congestive heart failure $\geqslant$ class II of the New York Heart Association Classification, hypersensibility to anthracyclines or previous hypersensibility reaction to Cremophor-containing products and serious concomitant illness or medical condition.

2.2. Administration of Caelyx

Caelyx was diluted in 250–500 ml of 5% glucose and administered as an intravenous (i.v.) infusion over 1 h at an initial dose of 35 mg/m^2, every 3 weeks. Routine prophylactic anti-emetic medication was not used. Since chemotherapy is usually poorly tolerated in patients with SCCHN, in the first phase of the study, 15 patients received a dose of 35 mg/m^2, every 3 weeks (group A), the following 11 patients were treated at 45 mg/m^2 (group B). Treatment was to be discontinued if requested by the patient or if documented tumour progression and/or unacceptable toxicity were observed.

2.3. Evaluation of response and toxicity assessment

Pre-therapeutic evaluation includedhistory and physical examination, performance status, tumour measurements, complete blood cell count with differential and platelet count, electrolytes and serum creatinine, bilirubin, aspartate and alanine aminotransferases, alkaline phosphatase, chest X-ray, 12 leads electrocardiogram (ECG) and LVEF by cardiac ultrasound. During the study, haematological assessment was repeated weekly and blood chemistry analyses were repeated before each cycle (every 3 weeks). Cardiac ultrasound was controlled after the completion of treatment for each patient. Toxicity was evaluated after each cycle according to the National Cancer Institute Common Toxicity Criteria.

Patients were assessable for response after receiving Caelyx and being observed for at least 4 weeks. Response evaluation was carried out weekly with a clinical examination and imaging evaluation (CT scan and/or MRI) was performed every 2 cycles according to established bidimensional response criteria [19].

3. Results

3.1. Patient characteristics

26 patients (24 males, 2 females) with good performance status and locally recurrent or metastatic differentiated SCCHN entered the study (Table 1). Most patients presented with local recurrences (17/26, 65%). All patients were pretreated by either radiation therapy alone and/or chemotherapy. Prior chemotherapy consisted of platinum-5-fluorouracil (5FU) or taxane-based regimen. No patient received prior anthracycline treatment.

3.2. Antitumour activity

Among the 26 patients (total: 87 cycles) entered in this study, 2 were not evaluable for antitumour activity (early death at day 2 of first cycle from a concomitant unexpected comorbidity: 1 patient, lost to follow-up: 1 patient). Among 24 evaluable patients, 4 patients (all in group A) had presented objective responses (17%, 95% confidence interval (CI) 0.5–32%). The antitumour activity was observed in patients with local recurrence in an irradiated area after 2 cycles of Caelyx (Fig. 1(a) and (b)), no objective response was observed in patients with distant metastasis. Among the 4 responding patients, 2 experienced necrosis of the bulk of the tumour. 8 patients presented tumour stabilization as their best response, including 4 long-term stabilisations (6, 6, 9 and 12 months). The median time to tumour progression and survival were 3.5 and 4.6 months, respectively.

Table 1
Patients characteristics

	Group A (35 mg/m^2)	Group B (45 mg/m^2)	Total
Number of patients included	15	11	26
Male/female	14/1	10/1	24/2
Median age, years (range)	54 (48–70)	52 (44–73)	52 (44–73)
WHO[a] performance status	0–2	0–2	0–2
Primary tumour			
Oropharynx	7	8	15
Oral cavity	2	3	5
Hypopharynx	4	0	4
Nasopharynx	1	0	1
Other (maxillary sinus)	1	0	1
Status at study inclusion			
Local recurrence	10	4	14
Metastatic recurrence	3	6	9
Local and metastatic recurrence	2	1	3
Prior therapy			
Radiation therapy	6	2	8
Chemotherapy	1	1	2
Radiation and chemotherapy	8	8	16

[a] World Health Organisation.

3.3. Toxicity

Among the 26 treated patients, 1 patient was not evaluable for toxicity because of early death (day 2 of first cycle). Fourteen patients were treated in group A (43 cycles) and 11 patients in group B (34 cycles). The median number of cycles was 3 (range 1–7) Toxicity results are summarised in Table 2. Haematological toxicity was mild with only 2 patients (one in group A and one in group B) presenting with grade 3–4 non-febrile neutropenia. No grade 3–4 thrombocytopenia was observed. Three patients presented with grade 3–4 anaemia, but 2 of these patients previously displayed grade 2 anaemia at the study inclusion. Non-haematological toxicities were mild to moderate, except for 2 episodes of grade 3 transient allergic reaction (headache and hypertension in 2 patients) and one grade 3 diarrhoea. No patient presented alopecia or acute cardiac toxicity considered related to the study drug during the course of the study.

Local complications in the irradiated area were represented by intratumour pain with or without facial oedema requiring antalgic treatment. Severe grade 3 necrosis was observed in 2 patients in group A. Moderate bleeding was reported in 2 patients (one in group A and one in group B).

4. Discussion

Recent formulations of pegylated liposomal doxorubicin (Caelyx) allow a reduced uptake of the compound by the reticulo-endothelial system, an extended duration of exposure and a reduced volume of distribution, thereby promoting tumour uptake. In this study, Caelyx was well tolerated up to 45 mg/m^2 with marginal Grade 3–4 toxicity and confirmed previous phase I reports [17], with no dose-limiting mucosal or cutaneous toxicity reported among the 11 patients treated at 45 mg/m^2. Cardiac toxicity or alopecia were not reported.

The majority of our study population had locoregional relapses in irradiated areas. Among the 24 patients evaluable for activity, 4 patients (all in group A) with a local relapse experienced an objective response (17%). In 2 patients, tumour shrinkage consisted of massive tumour local necrosis with ulceration (associated with bleeding in one patient). Pegylated liposomes

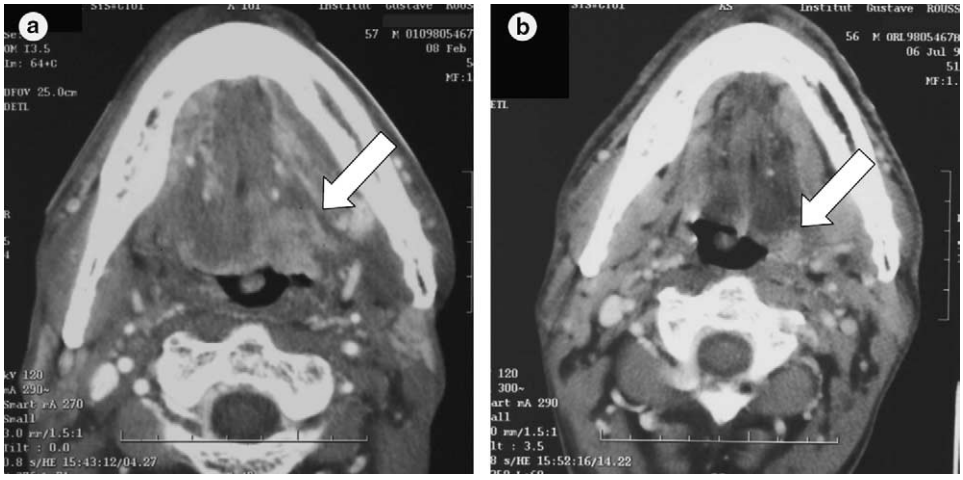

Fig. 1. Effects of Caelyx in a patient with locoregional relapse in an irradiated area. Panels a and b: epidermoid carcinoma of the oral cavity prior to and after Caelyx administration. The carcinoma displays an objective response in b.

Table 2
Maximal toxicity per evaluable patient ($N = 25$)

	Group A				Group B			
	Dose 35 mg/m^2 $N = 14$				Dose 35 mg/m^2 $N = 11$			
	G1	G2	G3	G4	G1	G2	G3	G4
Systemic toxicity								
Neutropenia	–	2	–	1[a]	–	–	1	–
Thrombocytopenia	1	–	–	–	1	–	–	–
Anaemia	4	5	1	1[b]	2	5	1[b]	–
Allergic reaction	–	2	2	–	–	–	–	–
Local reaction	2	–	–	–	–	–	–	–
Skin toxicity	–	–	–	–	2	–	–	–
Nausea-vomiting	2	–	–	–	1	4	–	–
Diarrhoea	1	3	1	–	2	1	–	–
Mucositis	2	3	–	–	4	3	–	–
Asthenia	1	3	–	–	–	4	–	–
Fever	–	–	–	–	2	–	–	–
Transaminase increase	1	1	–	–	1	–	–	–
Local complications								
Pain	3	1	1	–	–	1	–	–
Facial oedema check	1	1	3	–	–	–	2	–
Ulceration/necrosis	1	1	2	–	–	–	–	–
Haemorrhage	–	1	–	–	–	1	–	–

[a] Febrile episode occurring during Grade 4 neutropenia with negative bacterial sampling.
[b] Patients displaying Grade 2 anaemia at study inclusion.

have been shown to extravasate through leaky tumour vasculature and accumulate in the extravascular interstitial space between tumour cells [20]. Therefore, Caelyx might protractedly release doxorubicin in interstitial areas as liposomes diffuse slowly into the tumour tissue [21]. Prior high doses of radiotherapy might facilitate this process since late radiation-induced tissue modifications, including fibrosis, would establish intratumoural conditions that rapidly breakdown the extravased liposomes, facilitating doxorubicin radiation-recall effects, slowing down healing processes, and inducing tumour necrosis [22].

In summary, Caelyx was well tolerated up to 45 mg/m^2 and displayed moderate single agent activity against locally recurrent SCCHN. Due to a high tumour tissue distribution of the drug tumour necrosis, ulceration and bleeding can be induced. Careful utilisation of the drug is required for the treatment of tumours relapsing in irradiated areas.

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