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Phase II trial of pegylated-liposomal doxorubicin in the treatment of locally advanced unresectable or metastatic transitional cell carcinoma of the urothelial tract

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Abstract

34 patients with advanced unresectable or metastatic urothelial carcinoma who had not received prior chemotherapy for metastatic disease were treated with pegylated-liposomal doxorubicin (PLD) 50 mg/m^2 by a 1-h intravenous infusion (i.v.) every 4 weeks in a multi-institutional phase II trial. 6 of 30 evaluable patients had a partial response to treatment (20%; 95% Confidence Interval (CI), 8–39%) and seven patients had stable disease. Toxicities were primarily non-haematological, but severe palmar-plantar erythrodysesthesia (PPE), lethargy and anorexia were infrequent. Despite a high proportion of patients with poor prognostic features, PLD had clinically significant activity in urothelial cancer in this study. The activity and unique toxicity profile of this drug make it of interest for further study in advanced urothelials cancers in combination with other active agents.

Keywords: Bladder neoplasms; Urological neoplasms; Doxorubicin; Liposomes; Drug therapy

1. Introduction

Cisplatin-based combination chemotherapy induces remission in approximately 50% of patients with advanced unresectable or metastatic transitional carcinoma of the urothelial tract (TCC), often improving symptoms and prolonging survival. Cisplatin-based combinations such as methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) and cisplatin, methotrexate and vinblastine (CMV) have been considered standard chemotherapy regimens for TCC for almost 20 years [1]. Recently, both gemcitabine plus cisplatin and dose intensive M-VAC given with granulocyte-colony stimulating factor (G-CSF) have been shown to provide a similar disease control and survival benefits in comparison to standard M-VAC, but with less severe toxicity [2,3]. Unfortunately, progression of disease is inevitable for nearly all patients, and 80% of patients die within 2 years despite modern chemotherapy [4]. Half of TCC patients are over age 65 years, and age-related decline in renal function, diversion or obstruction of the urinary tract, a higher risk of cardiovascular toxicity, and other comorbidities also often complicate treatment. Thus, active agents with favourable toxicity profiles remain of interest. Doxorubicin has a pooled single agent objective response rate of 17% (95% Confidence Interval (CI), 12–23%), and neoadjuvant trials using doxorubicin-containing regimens have reported survival benefits [5,6].

Pegylated-liposomal doxorubicin (PLD) consists of doxorubicin contained within 80–90 nm dual compartment lipid vesicles with a polyethylene glycol coating [7]. The result is a pharmacokinetic profile quite different from conventional doxorubicin, with a plasma half-life

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of 2–3 days and a slow clearance rate (<0.1 l/h). Tissue distribution also differs; PLD accumulates preferentially in tissues having increased microvascular permeability, a characteristic often associated with solid tumour tissues. Not surprisingly, the toxicity profile of PLD is quite different as well. Myelosuppression and cumulative cardiotoxicity limit treatment with conventional doxorubicin. In contrast, palmar-plantar erythrodysesthesia (PPE) and mucositis are the dose-limiting toxicities with PLD and little myelosuppression, alopecia and cardiotoxicity are usually seen. PLD has not been studied in TCC, although liposomal daunorubicin has been studied with no responses reported in 15 evaluable patients [8].

The recommended dose of PLD is 50 mg/m^2 intravenously (i.v.) every 4 weeks [9]. Evaluation in other disease sites has consistently demonstrated a reduced toxicity compared with conventional doxorubicin. In a randomised trial comparing PLD with conventional doxorubicin in soft-tissue sarcomas, PLD caused less alopecia, myelosuppression and cardiotoxicity, without evidence of a reduced antitumour efficacy [10]. Phase III trials comparing PLD as a single agent with standard chemotherapy combinations in AIDS-related Kaposi's sarcoma and recurrent ovarian cancer also report a favourable therapeutic index [11–14]. In the present study, patients with previously untreated TCC were treated with PLD 50 mg/m^2 by i.v. infusion every 4 weeks. The primary endpoint was the objective response rate and secondary endpoints included response duration, toxicity and overall survival.

2. Patients and methods

2.1. Patients

Adult patients with a diagnosis of advanced unresectable or metastatic TCC of the urothelial tract were potentially eligible for this multicentre single-arm trial if they had received no prior chemotherapy for metastatic disease. Prior chemotherapy given as adjuvant, neoadjuvant or concurrent with radiotherapy was allowed if completed at least 6 months prior to study entry, and if no more than 180 mg/m^2 of doxorubicin or 270 mg/m^2 of epirubicin had been received. Patients were required to have bidimensional disease when assessed by conventional imaging techniques; and adequate performance status (Karnofsky $\geqslant$60%), life expectancy ($\geqslant$3 months), and adequate organ function including: left ventricular ejection fraction (LVEF) ($\geqslant$50% by radioisotope wall motion study), haemoglobin (>90 g/l), neutrophils ($\geqslant 1500\times\ 10^6$/l), platelets ($\geqslant 100\times 10^9$/l), serum creatinine $\leqslant$180 μmol/l (or creatinine clearance $\geqslant$0.83 ml/s), bilirubin ($\leqslant$32 μmol/l), and aspartate aminotransferase ($\leqslant$2 times upper normal limit or $\leqslant$5 times upper normal limit if the patient had documented liver metastases). Exclusion criteria included: congestive heart failure $\geqslant$New York Heart Association class II, uncontrolled infection, radiotherapy within 4 weeks, another active cancer (except superficial non-melanomatous skin cancer and carcinoma *in situ*), symptomatic brain metastases, and prior radiotherapy to more than one-third of the haematopoietic sites.

2.2. Study evaluations

Physical examination, complete blood count and differential, serum biochemistry, chest radiograph, electrocardiogram (ECG), abdominopelvic sonogram or computed tomographic (CT) scan, and evaluation of LVEF by radioisotope wall motion study scan were performed within 4 weeks of study entry. A complete blood count and differential was performed weekly while on therapy. Physical examination, toxicity evaluation and serum chemistries were done prior to each course of PLD. Response to therapy was evaluated following every two cycles of treatment. Repeat evaluation of LVEF was planned after a cumulative PLD dose of 500 mg/m^2.

2.3. Study treatment

PLD treatment in the study was offered to eligible patients prior to or as an alternative to standard cisplatin-based chemotherapy. PLD was administered as a one hour i.v. infusion at a dose of 50 mg/m^2 every 4 weeks for six cycles, toxicity permitting. Antiemetics and other supportive care measures were allowed as clinically indicated. 5-HT$_3$ receptor antagonist antiemetics were not routinely used, and prophylactic use of colony-stimulating factors was not permitted. Treatment was discontinued for disease progression, cardiotoxicity, persisting symptoms of PPE or stomatitis lasting at least eight weeks, grade 4 neutropenia occurring with three consecutive cycles despite dose delays and reduction, any other grade 4 toxicities, any other concerns for the patient's welfare, or at the patient's request. Patients considered to be benefiting from PLD could continue beyond six cycles at the discretion of the treating physician. Patients were given written information about the study and provided written informed consent. The study was reviewed and approved by the Research Ethics Board of each participating institution, and conducted in accordance with the Declaration of Helsinki.

2.4. Toxicity and dose modifications

Toxicity information was graded according to World Health Organization (WHO) criteria. PPE was graded and doses adjusted as described by Gordon and colleagues [15]. Mild erythema, swelling, or desquamation not interfering with daily activities was considered grade 1.

Interference with daily activities not precluding normal physical activities or small blisters or ulcerations <2 cm was considered grade 2. PPE interfering with walking, normal daily activities, or rendering patient unable to wear regular clothing was considered grade 3; and PPE causing infectious complications, hospitalisation or a bedridden state was considered grade 4. PLD doses were delayed one week for: $\geqslant$grade 2 neutropenia, grade 4 thrombocytopenia, and any other $\geqslant$grade 3 non-haematological toxicity. For grade 4 haematological toxicity, treatment was delayed until granulocyte count $\geqslant 1.5\times10^9$/l and platelet count $\geqslant 75\times10^9$/l. PLD doses were reduced 25% for: grade 4 haematological toxicity, increased total bilirubin that was $\leqslant 51$ μmol/l, or a second occurrence of $\geqslant$grade 3 non-haematological toxicity. PLD doses were reduced 50% if total bilirubin was increased >51 μmol/l unrelated to PLD in the previous cycle. Treatment with PLD was discontinued for granulocyte count $<1.0\times10^9$/l persisting 2 weeks beyond the next scheduled dose or total bilirubin increased >51 μmol/l considered related to PLD. If an infusion reaction occurred, the infusion was discontinued until symptoms resolved, and then resumed at 50% of the initial infusion rate.

2.5. Response assessment

Tumour dimensions were measured within 28 days prior to starting therapy and subsequently after every two cycles of PLD treatment. Responses were assessed according to WHO criteria, and were confirmed by repeat imaging at least 28 days from the first date of response. Bidimensionally measurable lesions had clearly defined margins and at least one diameter $\geqslant 0.5$ cm on chest radiograph, both diameters greater than the distance between cuts on CT scan, or were $\geqslant 2.0$ cm. Response duration was measured from the date of first observation of a durable response to the first date of documented progression or death. Time to progression was measured from the date of study entry to the date of disease progression or last follow-up. Overall survival was measured from the date of study entry to the date of death or last follow-up. For the primary endpoint, the evaluable patient population was defined as all patients meeting inclusion and exclusion criteria who received at least two cycles of study drug and completed all visits according to schedule. Patients with progressive disease during the first two cycles were considered evaluable. The intention-to-treat population was defined as all patients who received at least one dose of study drug, and this was also the evaluable population for safety.

2.6. Statistical considerations

The Gehan two-step procedure was used [16]. The lowest response probability implying that further investigation was warranted was considered to be 20%. In the first stage, 14 evaluable patients would be treated and if no responses were observed the study would be stopped; under these conditions the probability of rejecting a treatment with a response rate of at least 20% is less than 5%. If at least one response was seen in the first 14 patients, then additional patients would be added depending on the number of responses observed in order to estimate the therapeutic effectiveness with a standard error of 10%.

3. Results

3.1. Patients

Patients' characteristics are listed in Table 1. All 34 are included in the intent-to-treat analysis, and 33 in the safety analyses. 9 patients were older than 75 years and 11 had a Karnofsky performance status of less than 80%. All had TCC with the primary site in the urinary bladder (30 patients) or renal pelvis (5 patients); 1 patient had separate primaries in both sites. 16 patients had been treated surgically with curative intent for locally advanced TCC (12 cystectomy, 4 nephrectomy). 10

Table 1
Baseline patient characteristics

Characteristic	No.
No. of patients	34
Gender	
Male	26
Female	8
Age (years)	
Median (range)	67 (47–85)
$\geqslant$70 years	12
Karnofsky performance status	
Median (range)	85 (60–100)
<80	11
Primary site	
Bladder	30
Renal pelvis	5
Locoregional/lymph node	6
Distant metastases	28
Lymph nodes	18
Lung	11
Liver	9
Bone	5
Adrenal	4
Visceral metastases	21
Four or more sites of disease	12
Prior treatment	
Cystectomy	13
Nephrectomy	4
Neo/adjuvant chemotherapy	4
Adjuvant radiotherapy	1
Bladder radiotherapy (+concomitant cisplatin)	3 (2)

patients had presented with metastatic disease. The remaining 8 patients presented with locally advanced disease considered unresectable (5 patients), inoperable (2 patients), or who refused cystectomy (1 patient). 13 had liver and/or bone metastases (38%) and 6 (18%) had multiple visceral metastatic sites.

3.2. Treatment

A total of 125 doses of PLD for a median of 2.5 cycles (range 1–10 cycles) were administered to the 34 patients. 10 patients (29%) received only one PLD infusion. In 7 patients, treatment was discontinued after one cycle due to progressive disease and these patients were evaluable for response as early progressors. 2 patients discontinued treatment after one cycle because of pyelonephritis and anorexia considered unrelated to PLD; these patients were considered inevaluable for response. One patient died unexpectedly 5 days after the first PLD infusion (see details below); this patient was considered inevaluable for both response and toxicity, but this event is included as an adverse event. The mean cumulative dose was 178.5 mg/m^2 (median 150 mg/m^2) with a range from 50 to 500 mg/m^2. Planned dose intensity was 12.5 mg/m^2/week, and the delivered dose intensity was 11.4 mg/m^2/week (91.2%). 10 patients (29%) received 300 mg/m^2 or more. 11 patients received second-line chemotherapy after discontinuing PLD. One patient had a complete response to M-VAC.

3.3. Response

6 of the 30 evaluable patients responded (no complete responses, six partial responses) and 7 had stable disease for an overall objective response rate of 20% (95% CI 8–39%). The intention-to-treat response rate was 18% (95% CI 7–35%). The characteristics of the responding patients are summarised in Table 2. An additional patient met the radiological criteria for a partial response, but repeat imaging to confirm this was not completed. This patient is considered inevaluable for response, but is included in intention-to-treat and toxicity analyses as a non-responder. In addition to the 7 early progressors, 7 patients also had progression documented at the first response evaluation. 3 of 6 responding patients had hepatic metastases, including an 85-year-old man with Karnofsky performance status of 60 at baseline who had a near complete response. In total, 3 of 9 patients with hepatic metastases had an objective response documented by either abdominal sonogram (2 patients) or CT scan (1 patient). In addition, the patient with an unconfirmed response had hepatic metastases. None of the responding patients had received prior neo/adjuvant or concurrent chemotherapy. The median duration of response was 7.5 months (range 1.3–10.1 months). 33 patients have died, 32 due to disease progression and 1 due to uropsepsis on treatment; 1 patient was lost to follow-up at 4 months and is presumed to have died of disease progression. The median overall survival for all 34 patients was 7.5 months (range 0.6–27.6 months).

3.4. Toxicity

33 patients were evaluable for toxicity, and a total of 266 adverse events considered at least possibly, probably, or definitely related to PLD were seen (Table 3). Adverse events definitely, probably, or possibly related to PLD are reported as worst toxicity by patient including separate events of the same type and grade of toxicity occurring in the same patient. Two hundred and fifty-six (96.2%) of these events were non-haematological, and 30 (11.3%) were grade 3 or 4. One patient with a history of cardiovascular disease died suddenly at home following an episode of rigors five days after the first PLD infusion. Although the investigator's opinion was that death was due to bacteraemia originating in the urinary tract, and was not treatment-related, it is not possible to completely exclude this event as an early toxic death due to PLD. One patient developed febrile neutropenia. No grade 4 non-haematological toxicities were observed. Twenty-eight of 255 non-haematological events (11.0%) were of grade 3

Table 2
Characteristics of responding patients

Patient	Age (years)	Karnofsky performance status	Sites of disease	No. of courses	Response duration (months)	Survival (months)	Grade 3 toxicities
1	59	90	Bladder	6	1.3	25.7	
2	67	90	Liver, lymph nodes, pelvis, kidney	6	3.7	13.5	Rash Foot pain
3	74	90	Liver	6	6.0	12.3	Lethargy
4	85	60	Liver, lymph nodes, pelvis	8	6.1	12.6	
5	66	100	Lymph nodes, bladder	10	9.9	27.6	Abdominal pain
6	68	60	Lymph nodes	6	10.1	15.6	

Table 3
Adverse events considered definitely, probably, or possibly related to PLD

Toxicity	WHO toxicity grade			
	1	2	3	4
Haematological				
Neutropenia		2		2
Thrombocytopenia			1	
Anaemia	1	4		
Non-haematological				
PPE	7	4	3	
Stomatitis	9	7	2	
Skin	19	11	1	
Nausea/vomiting	18	14	2	
Anorexia/weight loss	6	7	3	
Lethargy	8	1	4	
Fever/chills/infection	16	6	1	
Respiratory	5	4	1	
Alopecia	9	2		
Diaphoresis/flushing	2	7		
Dehydration	3	4	1	
Diarrhoea	3	2		
Special sensory	9	3	1	
Constipation	4	5	1	
Neuromotor	5	2	3	
Pain/myalgia	8	4	2	
GI discomfort	2	2	1	
Oedema	3	3		
GU symptoms	2	2	1	

PLD, pegylated-liposomal doxorubicin; PPE, palmar-plantar erythrodysesthesia; GI, gastrointestinal; GU, genitourinary.

severity including: PPE, stomatitis, rash, nausea/vomiting, anorexia/weight loss, lethargy, infection, dyspnoea, dehydration, altered taste, constipation, weakness, pain/myalgia, dysphagia and urinary frequency. 14 patients experienced PPE, but only 3 developed grade 3 symptoms. PPE usually improved by withholding treatment for 1 week, and only 1 patient discontinued therapy because of PPE. Six hospitalisations occurred in 5 patients due to adverse effects. No clinical cardiotoxicity was observed; 1 patient had a drop in LVEF of 10% within the normal range after 10 cycles of PLD. There was one infusion reaction.

Treatment was discontinued due to adverse effects related to PLD in 6 patients. Other reasons for discontinuing treatment included progressive disease (21 patients), completion of protocol treatment (5 patients), patient's request (1 patient), and one death on treatment described above. 8 patients had 10 dose reductions and/or delays due to adverse events attributed to PLD. 4 of these patients had five dose reductions accompanied by treatment delay: 4 for PPE and one for grade 3 weight loss. The other four patients had five treatment delays without dose reductions: two for neutropenia, and the others for dyspnoea, elevated creatinine and diarrhoea.

4. Discussion

This study demonstrated an objective response rate of 20% with PLD in patients with previously untreated unresectable or metastatic TCC of the urothelium. This response rate is similar to conventional doxorubicin and epirubicin (pooled response rate 20% (95% CI 11–29%)) but less than other newer single agents such as paclitaxel (pooled response rate 38% (95% CI 23–54%)), gemcitabine (pooled response rate 25% (95% CI 16–34%)), and docetaxel (response rate 31% (95% CI 14–48%)), but this may be explained in part by differences in patient selection [17–24]. Eligible younger patients with a good performance status usually preferred cisplatin-based combination chemotherapy, and generally declined participation in this study. The median age of the study participants was 67 years, and over one-third were aged 70 years or older. The median age of patients in urothelial cancer chemotherapy trials is usually less than 65 years, even in large phase III trials, and age $\geqslant 70$ years is an independent adverse prognostic factor for time to treatment failure in urothelial cancers [2,3]. In addition, over 60% of patients in this study had visceral metastases, approximately 40% had hepatic and/or bone metastases, and one-third had a Karnofsky score <80 at entry. The median survival in this study was only 7.5 months consistent with the higher prevalence of these independent adverse prognostic factors [2,4]. Such patients would also be expected to have lower rates of objective response and higher toxicity with any type of therapy; but despite this, a clinically significant response rate and favourable toxicity profile were seen.

3 of 9 patients with hepatic metastases responded to PLD. In contrast, none of 5 patients with hepatic metastases responded to paclitaxel plus granulocyte colony-stimulating factor, 2 of 14 responded to gemcitabine, and 3 of 10 responded to docetaxel [20,23,24]. Phase I trials of PLD in combination with each of these drugs have demonstrated response rates ranging from 33 to 60% in patients with pretreated metastatic breast cancer [25–27]. Such combinations are of interest for patients unable to tolerate cisplatin, patients with compromised cardiac function, those who have previously received conventional doxorubicin, or as a component of second-line treatment in platinum-resistant patients. The unique toxicity profile of PLD makes its addition or substitution in regimens currently used first-line in advanced urothelial cancer feasible; for example, PLD has been combined with paclitaxel and cisplatin in a phase I study [28]. PLD may also be of interest in urothelial cancer as a radiosensitiser in bladder preservation protocols [29]. Further clinical trials of PLD-based combinations will be required to define its most appropriate roles in urothelial cancer.

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