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ORIGINAL ARTICLE

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Preclinical trial of doxorubicin entrapped in sterically stabilized liposomes in dogs with spontaneously arising malignant tumors

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Abstract *Purpose*: To prospectively evaluate the short-term toxicoses associated with pegylated-liposomal doxorubicin (Doxil) administered to dogs with measurable tumors of various histologic types and sites. Preliminary information regarding efficacy was also generated. *Methods*: A group of 51 dogs with histologically confirmed malignancies received a total of 103 Doxil treatments given i.v. every 3 weeks at dosages ranging from 0.75 to 1.1 mg/kg in the context of a phase I dose-escalation trial. Acute and short-term toxicities as well as tumor response and duration of response were characterized. *Results*: The maximally tolerated dose in tumor-bearing dogs was established as 1.0 mg/kg i.v. every 3 weeks. The dose-limiting toxicity was a cutaneous toxicity clinically resembling palmar-plantar erythrodysesthesia (PPES). An overall response rate of 25.5% was observed with five complete responders and eight partial responders. *Conclusions*: Doxil appeared to be well tolerated at dosages similar to those tolerated for free doxorubicin in tumor-bearing dogs. PPES was the dose-limiting toxicity encountered, rather than myelosuppresion as is the case with free doxorubicin in dogs. Doxil as a single agent may have a broad spectrum of activity and deserves further evaluation.

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Introduction

Historically, the chemotherapeutic agent doxorubicin (DOX) has been one of the most effective and broad-spectrum drugs available to physicians and veterinarians for the treatment of a variety of malignant tumors. The dose-limiting toxicities of DOX include myelosuppression and cardiotoxicity [1, 2]. Recently, in efforts to attenuate the dose-limiting toxicities of DOX, various liposome formulations have been utilized as DOX drug-carrier systems, and most have proven to reduce both the myelosuppressive and cardiotoxic sequelae [3–7]. A disadvantage of early liposome systems is their rapid clearance from the circulation as a consequence of sequestration within the mononuclear phagocyte system (MPS) which can damage this important host defense and prevent the active drug from reaching other sites of action [8, 9].

A novel means of avoiding MPS sequestration is through the use of sterically stabilized liposomes; so-called 'stealth' liposomes. These liposomes contain a small fraction of a polyethylene-glycol (PEG)-derivatized phospholipid which avoids MPS uptake and results in long-circulating liposomes which enhance the delivery of anticancer drugs to tumors [8, 9]. A doxorubicin-entrapped stealth liposome formulation, Doxil, has proven to be effective in decreasing cardiotoxicity, prolonging drug circulation times, and enhancing tumoricidal effects (when compared with free DOX) in a variety of tumor models [10–12].

For preclinical efficacy and toxicity studies of new chemotherapeutic agents, the canine spontaneous tumor model offers several advantages. First, tumors in client-owned companion animals are spontaneous tumors occurring in an outbred population and are

therefore a more realistic representation of tumors in humans than are laboratory animal models. Second, the time-course for tumor progression and antineoplastic therapy response is typically shorter than for tumors in humans. This time-course is both long enough to allow comparison of response times and short enough to ensure rapid accrual of data. Third, unlike laboratory animals, dogs share a common environment with humans. Fourth, as in humans, DOX is widely used in dogs and remains one of the most broad-spectrum drugs in our armamentarium. Finally, the pharmacokinetics of Doxil have been determined in the dog. In dogs and humans, Doxil has a longer half-life, slower clearance, and greater area under the concentration versus time curve when compared with free DOX, making it an attractive compound for evaluation of increased efficacy [8–10, 13]. The purpose of the study reported here was to prospectively evaluate the short-term toxicoses associated with Doxil administered to dogs with measurable tumors of various histologic types and sites in the context of a phase I clinical trial. Preliminary information regarding efficacy was also generated.

Materials and methods

Patient population

The study population comprised 51 client-owned dogs from the patient population presenting to the Veterinary Medical Teaching Hospital at the University of Wisconsin-Madison from October 1994 through September 1995. The patients' ages and body weights ranged from 1 to 16 years (mean 9.2, median 9 years) and 3.4 to 53 kg (mean 28.2, median 28 kg), respectively. Of the 51 dogs, 30 were female (26 neutered) and 21 were male (16 neutered). Clients were offered Doxil therapy for their companion animals in cases of advanced disease where no meaningful standard therapy existed or where standard therapy had failed. Histologic confirmation of diagnosis was procured in all 51 dogs. Each dog's tumor was staged according to the classification scheme of the World Health Organization [14]. Diagnostic methods employed varied depending on the histologic type of tumor, the anatomic location of the tumor and the clinical status of the dog. These included, but were not limited to, physical examination, complete blood count (CBC), serum biochemical analysis, urinalysis, and radiographic studies. Dogs were eligible for entry provided they had adequate hematologic and serum biochemical parameters to undergo chemotherapy and were free of complicating concurrent disease. Dogs entered had not received chemotherapy within 2 weeks prior to Doxil therapy, nor was concurrent therapy used. All dogs had gross measurable disease at the time of entry. All tumors were measured either by physical examination (i.e. caliper measurements) or by examination of radiographs.

Tumor histology

A total of 21 tumor types were represented (Table 1). In cases of non-Hodgkin's lymphoma (NHL), all dogs were heavily pretreated with a standard combination chemotherapy protocol [15], were out of remission, and clinically chemoresistant to free DOX. Five dogs were entered subsequent to tumor recurrence following surgical excision. Five others were entered following treatment failures with several other chemotherapeutic agents.

Drug

Doxil is a DOX-containing liposome preparation provided by Sequus Pharmaceuticals (Menlo Park, Calif.). It has the following lipid composition (expressed as percent mole ratio): hydrogenated soybean phosphatidylcholine (56.2), cholesterol (38.3), and polyethylene-glycol (M_r 1, 900) derivatized distearoyl-phosphatidylethanolamine (5.3) [10]. DOX is encapsulated in the liposome internal aqueous space at a drug-to-phospholipid ratio of approximately 150 μg/μmol. More than 98% of the drug is in the encapsulated form. Doxil was administered undiluted at a concentration of 2 mg DOX/ml. The dose was measured and expressed on the basis of Doxil's DOX content. Doxil was administered intravenously (i.v.) over a 5–10-min period every 3 weeks until the dog developed progressive disease or the animal's quality of life decreased to a point deemed unacceptable by the owner and attending veterinarian.

Treatments

A total of 103 treatments were given at the following dosages (mg/kg) 0.75 ($n = 23$), 0.8 ($n = 4$), 0.85 ($n = 16$), 0.9 ($n = 8$), 1.0 ($n = 49$) and 1.1 ($n = 3$); mean and median 0.9 mg/kg. The objective was to increase the dosage of Doxil to a point where dogs would have $\leq 5\%$ prevalence of serious, potentially life-threatening toxicoses; this was considered the maximal amount of toxicoses that owners and veterinarians would consider acceptable in the average clinical practice. Two additional dogs did not receive their entire dose and were dropped from the study owing to acute reactions during drug delivery. Of the 51 dogs, 19 received one treatment, 20 received two, 8 received three, 2 received four, 1 received five, and 1 received seven giving a mean and median of two treatments per dog.

Toxicity assessment

A CBC and platelet count were obtained prior to each treatment, and when clinically feasible, on day 7 following each dose of Doxil. At each 21-day reevaluation visit, a thorough history and physical examination were performed to determine any clinically adverse effects of the drug treatment.

Parameters for evaluation of therapeutic response

Tumors were measured in millimeters for each dog immediately prior to Doxil treatment and then again 21 days following each drug administration. The measurements consisted of three-dimensional caliper measurements in accessible tumors, or in the case of radiographs, the longest diameter and a perpendicular diameter at the widest portion of each tumor. A complete response (CR) was defined as complete regression of all measurable tumor. A partial response (PR) was defined as a $\geq 50\%$ decrease in the measurable tumor volume and no evidence of new tumor. Stable disease was defined as $< 50\%$ decrease or $< 25\%$ increase in the measurable tumor volume, without the development of new lesions. Progressive disease was defined as $> 25\%$ increase in the measurable tumor volume, or the appearance of new neoplastic lesions. The duration of response was defined as the time from achievement of response until subsequent progression of disease or death.

Table 1 Tumor histology and response to Doxil therapy

Tumor/type	No. treated	CR PR	Median remission time (days) CR PR	No. treated/dose (mg/kg) 0.75	0.8–0.9	1.0–1.1
Mycosis fungoides	9	3	90 (21–340)	5	1	3
		1	60			
Anal gland adenocarcinoma	5	0		1	4	
		1	50			
Non-Hodgkin's lymphoma[a]	4	0		1	3	
		1	21			
Osteosarcoma	4	0		3	1	
		0				
Malignant melanoma	3	0			3	
		0				
Mammary gland carcinoma	3	0		1	2	
		1	74			
Hemangiosarcoma	3	1	31		2	1
		0				
Squamous cell carcinoma	2	0				2
		1	81			
Thymoma	2	0				2
		0				
Mast cell tumor	2	0			1	1
		0				
Anaplastic sarcoma	2	0		1	1	
		1	51			
Malignant histiocytoma	2	1	160	1		1
		0				
Fibrosarcoma	2	0				2
		1	45 +			
Transitional cell carcinoma	1	0				1
		0				
Thyroid carcinoma	1	0				1
		0				
Mesenchymoma	1	0		1		
		0				
Neurofibrosarcoma	1	0			1	
		1	60			
Schwannoma	1	0		1		
		0				
Pulmonary adenocarcinoma	1	0			1	
		0				
Sweat gland adenocarcinoma	1	0		1		
		0				
Multiple myeloma	1	0				1
		0				

[a] All heavily pretreated with combination chemotherapy, resistant to free doxorubicin

Results

Toxicities

No significant neutropenia or doxorubicin-associated cardiomyopathy were observed in any animal. Two dogs did not receive their scheduled dosage because of clinically significant acute reaction during drug delivery characterized by hypersalivation, prostration, pale mucous membranes, and sinus tachycardia. Both clients withdrew their dogs from study following this reaction; however, two subsequent dogs displaying similar acute reactions at the time of initial treatment were managed by pretreatment with diphenhydramine and slowing of the infusion rate to 0.5 ml/min. These dogs tolerated all subsequent treatments without incident. One dog died unexpectedly and acutely 10 days following its second dose of Doxil without premortem clinical signs. No necropsy was allowed in this case. In all other dogs, toxicity at the dosages used were limited to the skin and the gastrointestinal tract.

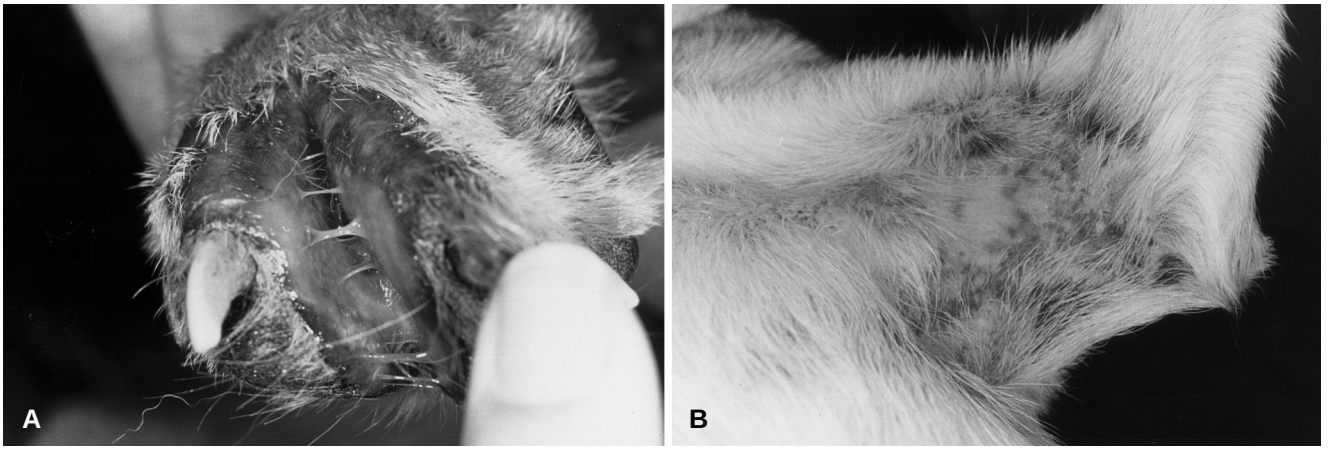

Fig. 1 **A** Cutaneous toxicity involving the paw of a dog 3 weeks following three treatments of Doxil (1 mg/kg every 3 weeks). Note alopecia, ulceration, and exudation between and around the digits. **B** Cutaneous toxicity involving the skin of the axilla in a dog following two treatments of Doxil (1 mg/kg every 3 weeks). Alopecia, erythema, and crusting can all be noted

Cutaneous toxicity

Of the 51 dogs, 10 (19.6%) developed cutaneous reactions ranging from mild erythema, hyperemia, edema, and alopecia to severe crusting and ulceration primarily in the axilla, inguinal region and the skin surrounding the footpads (Fig. 1). In four dogs, lameness associated with apparent paw discomfort while weight-bearing was noted. In four cases with cutaneous toxicity, histologic assessment was performed on skin lesions (Fig. 2). The most significant histologic features included follicular atrophy, perifollicular fibrosis, widespread and multifocal follicular necrosis often with associated granulomatous inflammation and marked pigmentary incontinence. Apocrine gland ectasia with scattered vacuolization or necrosis of apocrine gland epithelial cells was observed in all cases. Other features included superficial hyperkeratosis, orthokeratosis, and follicular hyperkeratosis with superficial plugging. Two cases also had evidence of perivascular to interstitial dermatitis with eosinophils and mast cells and superficial edema. Eight dogs required dose modifications (delay or decrease) because of skin reactions. Skin reactions were more likely after two or more doses and were observed more commonly in dogs receiving dosages of 1 mg/kg or more.

Gastrointestinal toxicity

Of the 103 Doxil treatments given, 7 (6.8%) resulted in mild, self-limiting inappetence, 5 (4.9%) resulted in mild (i.e. not requiring medical intervention) emesis, 14 (13.6%) resulted in mild transient diarrhea or colitis developing 4 to 7 days following treatment, while 2 (1.9%) resulted in significant emesis and diarrhea requiring hospitalization and fluid replacement therapy.

Therapeutic response

Response rates and duration of response are presented in Table 1. An overall response rate of 25.5% was observed including five CRs and eight PRs. The five dogs achieving CR included three with mycosis fungoides, one with oral hemangiosarcoma with pulmonary metastasis, and one with malignant histiocytosis with regional lymph node metastasis. The eight dogs achieving PR included one each with mycosis fungoides, neurofibrosarcoma, anaplastic sarcoma, mammary gland adenocarcinoma, anal sac adenocarcinoma, fibrosarcoma with lung metastasis, and multiple cutaneous squamous cell carcinoma with lung metastasis. Of the five dogs that had failed previous chemotherapy, one response was noted: a dog with NHL previously resistant to free DOX.

Discussion

The acute and short-term toxicities associated with Doxil administration to dogs with a variety of spontaneously arising tumors was evaluated in a dose-escalating fashion. During drug infusion, acute toxicities were noted in four dogs characterized by signs compatible with hypotension. In two cases where client approval was given, continuation of therapy was readily accomplished following diphenhydramine pretreatment and slowing of the infusion rate. Similar acute reactions have been reported in a small proportion of humans receiving Doxil [16].

With delivery every 3 weeks, the maximally tolerated dose (MTD) of Doxil appeared to be 1 mg/kg (DOX equivalent). This MTD is similar to that of free DOX in tumor-bearing dogs [1]; however, the dose-limiting toxicities are different for Doxil when compared to free

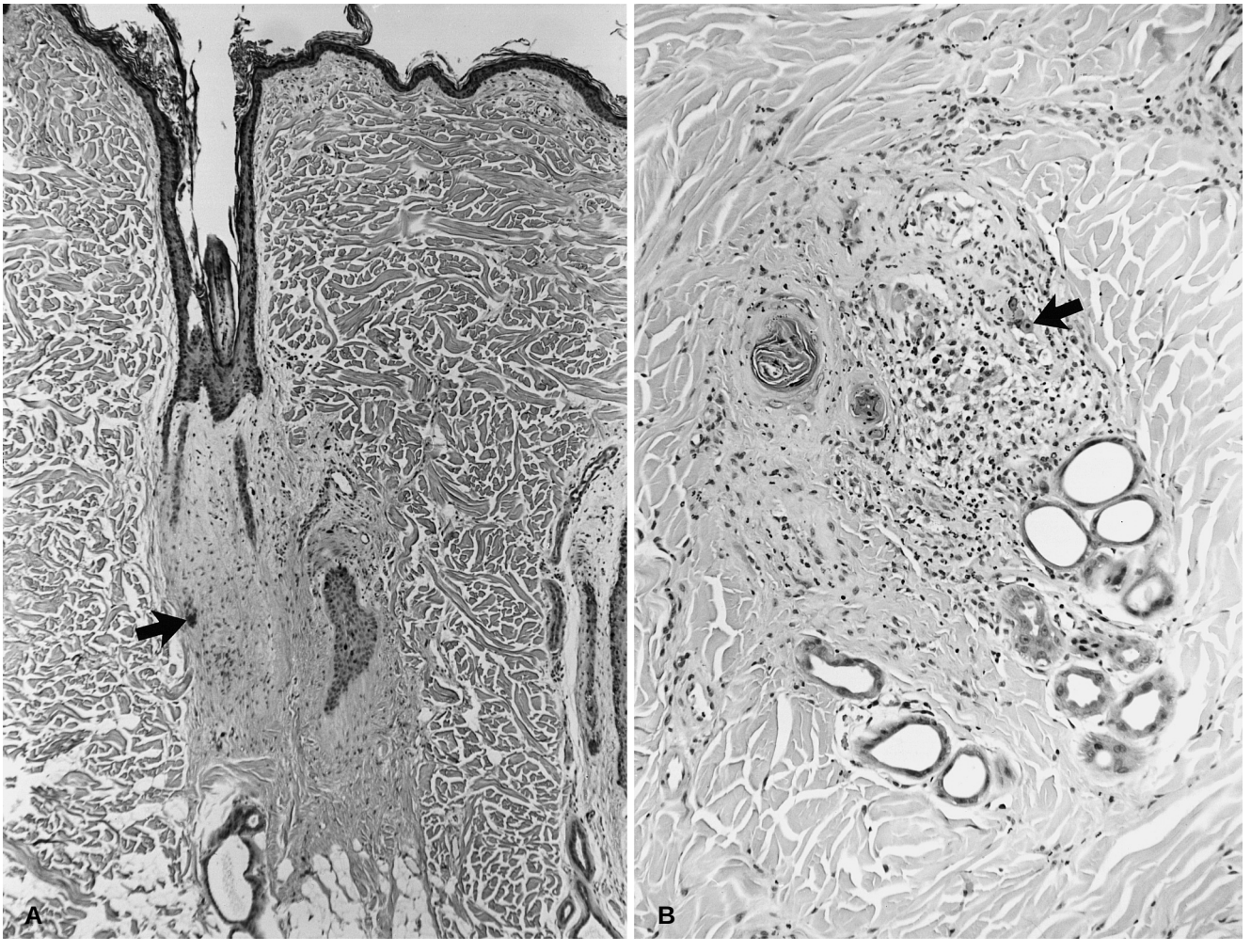

Fig. 2A, B Histology of cutaneous lesions in a dog 3 weeks following two treatments of Doxil (1 mg/kg every 3 weeks). **A** Follicular atrophy in the basilar half with multiple remnants of follicular papillae (*arrow*) enmeshed in perifollicular fibrosis. Note hyperkeratosis of the superficial epidermis and hyperplasia and hyperkeratosis in the superficial hair follicle (×12.5). **B** Follicular necrosis with associated granulomatous inflammation and interspersed residual epithelial cells (*arrow*) (×31.25)

DOX. While myelosuppression and to a lesser extent gastrointestinal toxicities are the dose-limiting short-term toxicities associated with DOX, no significant myelosupression was noted in dogs treated with Doxil in our study and gastrointestinal toxicity was observed less commonly than has been documented for native DOX [1]. The dose-limiting toxicity of Doxil observed in tumor-bearing dogs was a cutaneous reaction characterized by skin changes ranging from mild erythema, hyperemia, edema and alopecia, to severe crusting, ulceration and epidermal necrosis. Lesions occurred primarily in the skin of the paws, axilla and inguinal region. Lesions were self-limiting and typically resolved in 1–2 weeks following development.

The cutaneous toxicities described closely resemble palmar-plantar erythrodysesthesia (PPES) or hand-foot syndrome, a poorly understood syndrome recognized in humans undergoing long-term continuous infusions with various chemotherapeutic agents [10, 16–22]. It is theorized that continuous infusions result in PPES as a result of prolonged drug circulation times. Because the stealth properties of Doxil also result in prolonged circulation times, it is likely that a similar phenomenon is occurring. An alternate possibility is that Doxil may localize in skin to a greater degree than free DOX. The high frequency of antitumor response observed in dogs with mycoses fungoides could arguably be indirect evidence for such a phenomenon. PPES has also been documented as a significant toxicity in human patients receiving Doxil and often precludes repeated administration [11, 16]. PPES can have therapeutic consequences as it necessitates treatment delays or discontinuation, often at the expense of antitumor therapy.

In phase I human trials, PPES has been determined to be the dose-limiting toxicity for repeated dosing [16]. In humans, PPES is not steroid responsive. However, anecdotal reports have suggested that

oral pyridoxine (vitamin B_6) therapy may alleviate or reverse PPES in patients receiving fluorouracil and taxotere [23–25]. No histopathologic analysis has been undertaken on PPES lesions in humans; however, such an analysis could be important to elucidate the pathogenesis of this syndrome. Histologic changes observed in four dogs developing PPES-like reactions revealed significant follicular and perifollicular changes with associated perivascular and interstitial dermatitis. These biopsies represented fairly late changes, however, and we are presently procuring pre- and posttreatment cutaneous biopsies from dogs now receiving Doxil in our clinic to elucidate progression and further characterization of PPES.

We feel that dogs with spontaneously arising malignancies that are undergoing Doxil therapy would serve as an excellent model to provide insight into the histologic changes associated with PPES as well as prospectively evaluating the efficacy of agents to prevent PPES development. If the development of PPES can be abrogated, it is likely that the MTD can be significantly increased. A recent study demonstrated that Doxil-induced PPES in tumor-free laboratory dogs is related to dose intensity, with lower doses and longer dose intervals being associated with significantly reduced incidence and severity of this cutaneous toxicity [26].

While the primary focus of this study was to characterize short-term toxicities associated with Doxil, some preliminary information regarding antitumor activity may be suggested. The overall response rate of 25.5% is comparable to other anthracene antibiotic class chemotherapeutic agents such as doxorubicin and mitoxantrone used in similar phase I trials in tumor-bearing dogs [27, 28]. The evaluation of the limited response rates in this study must be done with the understanding that several dosages and various numbers of treatments were used. The relationship between dosage and response rate could not adequately be evaluated owing to the small number in each group. Additionally, all dogs in the study had bulky disease at the time of entry and the response rate with antitumor drugs is inversely proportional to the volume of tumor present. One of four dogs with NHL that had failed previous free-DOX therapy did achieve a short partial remission following Doxil therapy. This response may have been a result of altered pharmacokinetics inherent in the Doxil formulation or the possibility that its properties may have somehow overcome drug resistance factors present in the tumor.

Although the results of this study must be evaluated with care owing to the small number in each tumor group, it appears that Doxil as a single agent may have a broad spectrum of activity. This observation, along with the knowledge that liposome encapsulation significantly abrogates myelosuppression and cardiotoxicity when compared to free DOX, provides justification for further exploration of the efficacy of specified dosages of the drug in tumors of various histologic types.

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