Pergamon

European Journal of Cancer Vol. 31A, No. 12, pp. 2093–2098, 1995
Elsevier Science Ltd
Printed in Great Britain

0959-8049(95)00446-7

Original Paper

Intralesional Sustained-release Chemotherapy with Therapeutic Implants for Treatment of Canine Sun-induced Squamous Cell Carcinoma

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Squamous cell carcinoma (SCC) is the most frequently reported malignant epithelial tumour in dogs. Canine sun-induced SCC represents a useful animal model to evaluate new therapeutic modalities for possible human applications. We evaluated the safety and efficacy of treating sun-induced SCC in dogs with intralesional sustained-released chemotherapeutic gel implants that contained collagen, epinephrine (epi), and either 5-fluorouracil (5-FU) or cisplatin (CDDP). Dogs with large, single SCC or fields of multiple SCC were treated with 5-FU/epi gel for a minimum of three weekly injections. Dogs without a complete response were then treated with CDDP/epi gel for a minimum of three weekly treatments. We treated from one to 11 primary, recurrent, or refractory SCC per dog (tumour size 0.2–92.4 cm^2; mean cumulative tumour area of 40.7 cm^2 per dog). All dogs had at least 50% reduction in cumulative tumour area after treatment with 5-FU/epi gel. More than half (seven of 13) had complete resolution of SCC after treatment with 5-FU/epi gel or CDDP/epi gel. Minimal local tissue reactions were noted; no systemic toxicity occurred. Sustained-release chemotherapy using intralesional 5-FU/epi gel and CDDP/epi gel therapeutic implants is effective in treating canine sun-induced SCC of the skin.

Key words: canine squamous cell carcinoma, intralesional sustained-release chemotherapy
Eur J Cancer, Vol. 31A, No. 12, pp. 2093–2098, 1995

INTRODUCTION

THE MOST common sites of tumour in the dog are the skin and subcutaneous tissues [1, 2]. Squamous cell carcinoma (SCC) is the most common type of malignant epithelial neoplasm in the dog [1–3]. As in humans, chronic exposure to sunlight causes actinic skin damage that can ultimately result in SCC. Several breeds of dog with lightly pigmented skin on the sparsely haired regions of the abdomen and inner thighs appear to be at increased risk. Dogs sunbathe by lying on their backs, exposing their abdomens to UV radiation, which induces premalignant and malignant changes over the course of several years [4]. Typically, these sun-induced SCCs are well differentiated and have low metastatic potential [1, 5]. Thus, the dog is a useful model for investigating novel therapeutic approaches to the treatment of similar lesions in humans [6, 7].

Traditional forms of therapy for SCC in dogs have included surgical ablation and external-beam radiotherapy. Other treatments have been reported, including cryotherapy, local hyperthermia, topical dinitrochlorobenzene immunotherapy, and topical or systemic 5-fluorouracil (5-FU) chemotherapy. These treatment modalities have had varying degrees of success [1, 5], and are associated with a high rate of local tumour recurrence and new tumour formation in actinically damaged skin. Most recently, retinoids have been used with some success either alone [6] or in combination with local hyperthermia [7] to induce regression of multiple SCC lesions.

Therapeutic implants consist of a protein carrier matrix, a vasoactive agent (epinephrine) and a chemotherapeutic drug [8, 9]. The biodegradable matrix is a gel made of buffered, purified, sterile, non-pyrogenic bovine collagen that acts as a mechanical repository for drug which diffuses into the tissues [8–10]. This intralesional drug delivery format results in a higher tumour-to-plasma drug ratio over a more prolonged period than can be achieved with standard systemic drug administration or

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Revised 5 Jun. 1995; accepted 12 Jun. 1995.

by administration of free drug intralesionally [8–10]. Drug retention in the tumour bed is enhanced by the addition of epinephrine, which limits diffusion by causing vasoconstriction. In experiments with murine models, we found that the three-component implant (i.e. chemotherapeutic drug, epinephrine and collagen) was much more effective than implants that contained only one or two of the components [11].

Therapeutic implants have been used to treat a variety of tumours in cats, dogs and horses [12, 13] and to treat human basal cell carcinomas [14]. In this study, 5-FU and cisplatin (CDDP) were used to treat large areas of sun-induced SCC in dogs. The objectives of the study were to assess the safety, efficacy and feasibility of 5-FU and CDDP therapeutic implants in the treatment of canine SCC.

MATERIALS AND METHODS

Dogs

All dogs were referred for treatment of primary, recurrent or refractory squamous cell carcinoma. Tumours were classified as being sun-induced, based on the characteristic location in the lightly pigmented areas of skin without hair. Dogs eligible for study had measurable, histologically confirmed SCC lesions. Dogs with local lymph node involvement or systemic dissemination of SCC were excluded, as were dogs with terminal illnesses. Consent was obtained from all owners, as well as a commitment to return dogs for follow-up evaluations.

Investigational agents

The therapeutic implants (Matrix Pharmaceutical, Inc., Menlo Park, California, U.S.A.) consist of an injectable purified bovine collagen (collagen gel, Koken Co., Ltd., Tokyo, Japan), epinephrine (epi) (Adrenaline Chloride solution, Parke-Davis, Morris Plains, New Jersey, U.S.A.), and either 5-FU (Quad Pharmaceuticals, Inc., Indianapolis, Indiana, U.S.A.) or CDDP (Platinol, Bristol-Myers, Evansville, Indiana, U.S.A.) as the cytotoxic agent. The gel formulations used in this study contained both collagen (20 mg/ml) and epi (0.1 mg/ml) and either 5-FU (30 mg/ml) in the 5-FU/epi gel or CDDP (3.3 mg/ml) in the CDDP/epi gel.

Therapeutic implants were prepared by combining the components using a mixing adapter between two Luer-lock syringes. Implants were mixed just before use. Appropriate biosafety precautions were taken for preparing and administering implants, including the use of latex gloves and protective eye wear.

Study design

Each dog underwent a pretreatment evaluation consisting of medical history (including prior therapy for SCC), complete blood count, urinalysis, serum chemistry and body weight. Diagnosis of SCC was made after histological examination of biopsy specimens obtained from representative lesions.

All dogs were injected while under general anaesthesia. The injections were performed using 22- or 25-gauge needles on Luer-lock syringes in a fanning pattern to ensure even distribution of the therapeutic gel throughout the lesion. Lesions were injected until they appeared saturated with the gel, as judged by signs of tumour blanching, tumescence or leakage of implant gel from the surface of porous tumours. The dose of cytotoxic agent used for assessment of tumour response was the amount injected, as leakage of gel from the tumour surfaces was minimal.

Lesions were treated weekly until complete tumour resolution or until maximum response. For tumours that decreased in area by 50% or more after three weekly 5-FU/epi gel implants, treatment was continued until complete response or until no further reduction in tumour area was apparent after two further weekly injections. At that point, tumours without complete responses were then treated with CDDP/epi gel implants for a minimum of three injections or until complete response.

Efficacy and safety evaluations

The tumours were measured (length and width) using Vernier calipers at baseline and before each treatment at weekly intervals during the treatment period. Cumulative tumour area was calculated as the sum of the product of two-dimensional measurements of all lesions on a patient. After completion of the study period, dogs were followed up for as long as possible, and tumour-free survival and rates of relapse were assessed. Tumour responses were scored for treatment efficacy according to the following criteria: complete response (CR) when clinical evidence of disease (at all treated sites) could no longer be detected; partial response (PR) when the sum of all measurable tumour areas was reduced by $\geq$ 50% but $<$ 100%; and no response (NR) when the tumour either did not decrease by at least 50% or was progressive during the course of therapy.

The presence and severity of local cutaneous reactions were evaluated at each treatment visit. Investigators looked for the following tissue reactions: erythema, swelling, desquamation, scab, ulceration and necrosis. Necrotic tissue was debrided or excised and oral antibiotics were administered. Animals were weighed each week, and owners were requested to observe the dogs for evidence of systemic adverse effects. Dogs with clinical signs of illness, including lethargy, anorexia, fever, emesis, neurological abnormalities and change in water consumption, urination or stool, were then evaluated with complete blood counts and serum chemistry panels.

RESULTS

Thirteen dogs were treated in this study (Table 1). Dogs presented with one to 11 large, single SCC or fields of multiple SCC. Results for dogs with multiple lesions were reported as the sum of the area of all lesions treated (cumulative tumour area). The mean cumulative tumour area treated was 40.7 $\pm$ 37.4 cm^2 ($\pm$ standard deviation) per dog (range 1.2–102.2 cm^2). The dogs were Dalmatian and Dalmatian crosses (eight dogs), English bull terriers (two dogs), a Boston terrier, a pit bull terrier and an English pointer. Their ages ranged from 4 to 13 years (mean 7.8 years). These dogs were outdoor pets and thus had lifelong exposure to UV radiation. All but three dogs had histologically confirmed SCC present for more than 6 months (mean 21.9 months) before entry in this study, with an overall range of tumour duration of 1–65 months. Two dogs were previously untreated, and 10 dogs had new or recurrent lesions after previous surgical excision. Three dogs had lesions unresponsive to repetitive treatment with topical 5% fluorouracil cream.

Sites of involvement were the abdomen, medial thigh and flanks. SCC lesions were frequently multiple and consisted of erythematous, ulcerated plaques, small nodules, and larger, infiltrating tumour masses. Dogs also had multiple actinic keratoses on the lightly pigmented, hairless skin. All ulcerated or nodular SCC lesions present on each dog were treated with the intralesional therapeutic implants. Lesions assessed clinically to be premalignant, such as cutaneous horn or non-ulcerated actinic keratoses, were not treated. The 5-FU/epi gel implants were administered at weekly intervals until maximum tumour

Table 1. Intralesional chemotherapy of canine SCC using 5-FU/epi gel and CDDP/epi gel therapeutic implants

Dog*	Breed	Initial cumulative tumour area (cm^2)	No. of lesions (range of lesion area, cm^2)	Cumulative drug dose and response†						Disease-free interval‡ (weeks)	Disease-free survival§ (weeks)
				5-FU/epi gel			CDDP/epi gel				
				Total 5-FU dose (mg) (no. treatments)	5-FU dose (mg/cm^2)	Response	Total CDDP dose (mg) (no. treatments)	CDDP dose (mg/cm^2)	Response		
1	Dalmation	83.1	6 (0.24–41.2)	401 (6)	4.8	CR	—	—	—	345	345 D, UR
2	Dalmation	4.9	2 (0.7–4.2)	102 (2)	20.8	CR	—	—	—	160	160 K, MET
3	Dalmation	1.2	1	558 (7)	465.0	CR	—	—	—	60	60 LTF
4	Dalmation cross	31.7	2 (11.9–19.8)	75 (1)	2.4	CR	—	—	—	461	461 K, UR
5	Boston terrier	3.9	2 (0.2–3.7)	81 (2)	20.8	CR	—	—	—	11	11 K, UR
6	Dalmation cross	1.6	3 (0.2–0.7)	210 (3)	131.3	PR	1.8 (3)	1.1	CR	195	195 LTF
7	Pit bull	12.3	6 (0.2–6.6)	172 (3)	14.0	PR	4.8 (3)	0.4	CR	164	164 LTF
8	Dalmation	1.5	2 (0.2–1.1)	111 (5)	74.0	PR‖	—	—	—	0	91 K, PD
9	Dalmation	4.4	2 (1.1–3.3)	117 (2)	26.6	PR‖,¶	—	—	—	0	90 D, UR
10	Bull terrier	59.0	11 (0.5–11.0)	363 (3)	6.2	PR‖	—	—	—	0	53 K, PD
11	Dalmation	26.3	2 (7.5–18.9)	402 (6)	15.3	PR	6.0 (2)	0.2	PR¶	0	268 D, UR
12	Bull terrier	102.2	4 (0.7–92.4)	834 (5)	8.2	PR	40.0 (2)	0.4	PR	0	9 K, PD
13	English pointer	88.7	3 (1.2–64.2)	767 (7)	8.6	PR	21.6 (2)	0.2	PR¶	0	87 LTF

*Prior treatments: Before implant therapy, 10 dogs were treated surgically, and three were treated with topical 5-FU; two dogs did not undergo any prior therapy. †CR, 100% complete clinical response; PR, ⩾ 50% to < 100% decrease in tumour area. ‡From completion of implant therapy. §Documented survival from completion of implant therapy. D, died, UR, unrelated to SCC; K, killed; MET, metastatic SCC; PD, progressive disease; LTF, lost to follow-up. ‖Removed from study at owners' request before progressing to CDDP/epi gel treatment. ¶Dogs were cured by surgical excision of the tumour(s) after the tumour area was decreased by implant therapy.

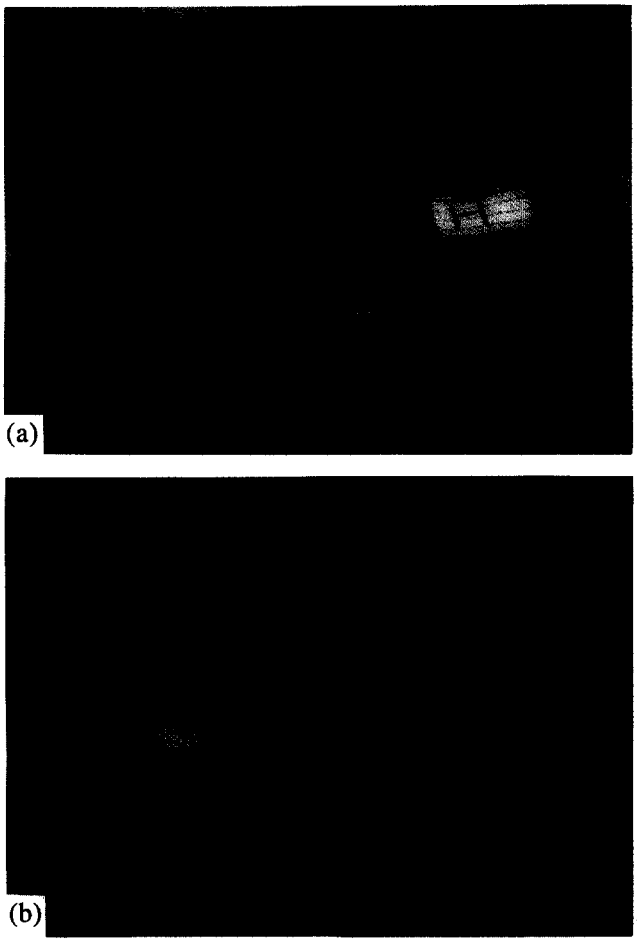

Figure 1. (a) Dog 1 had a field of superficial SCC lesions (cumulative area = 83 cm^2) that had failed to respond to 8 months of therapy with topical 5-FU (applied to all lesions once every 5 days). (b) A complete response was noted after 6 weekly treatments with 5-FU/epi injectable gel (401 mg 5-FU). The erythematous papules are due to flea bite allergy.

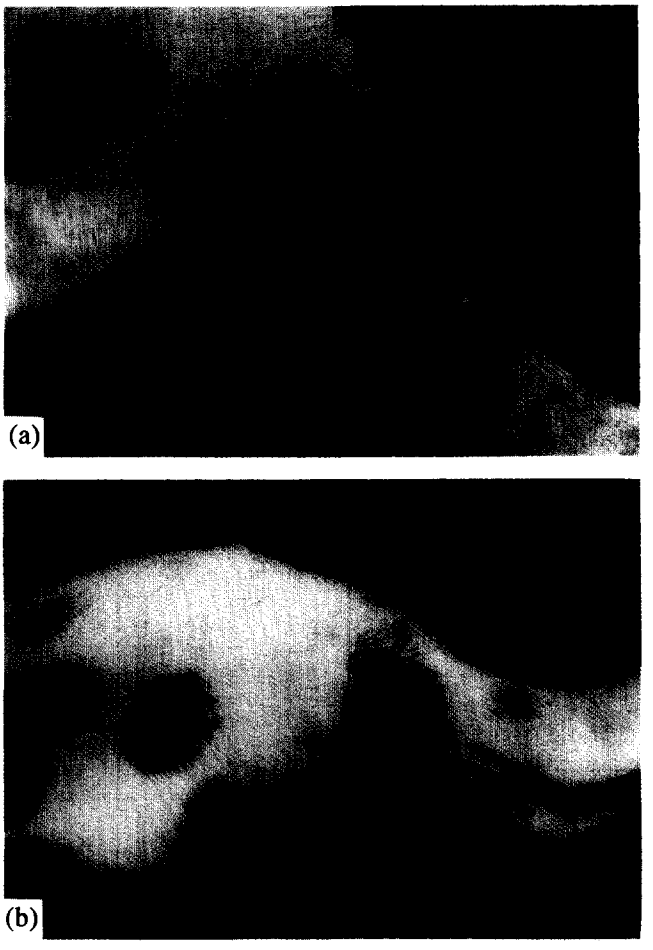

Figure 2. (a) Dog 4 before therapy showing a 32 cm^2 SCC on the medial thigh. (b) A complete clinical response was achieved with 5-FU/epi injectable gel (75 mg 5-FU) delivered in a single treatment.

response was achieved. A mean of five weekly therapeutic implant gel treatments (range 1–7) was administered per dog. The average cumulative dose of 5-FU was 296.7 ± 71.5 mg (range 75–834 mg). Five dogs were treated with CDDP/epi gel implants after the 5-FU/epi gel implants failed to induce further reduction in tumour area. A mean total dose of 13.1 ± 8.5 mg CDDP was delivered to these dogs in a mean of 2.4 treatments (a range of 1.8 to 40 mg CDDP was delivered in two to three treatments). With the exception of dog 12, at no time did dogs receive a dose of 5-FU or CDDP in the gel implants that was equivalent to the standard systemic canine chemotherapeutic dose based on body surface area.

Tumour responses

Squamous cell in all 13 dogs had a 50% or greater reduction in cumulative tumour area (PR + CR). Most dogs with multiple SCC had complete resolution of individual lesions; dogs were assessed to have a PR unless all lesions were resolved. Seven of these dogs (54%) had complete responses (Table 1). Dogs with CR had from one to six lesions with an initial cumulative tumour area ranging from 1.2 to 83.1 cm^2. Five of these dogs (dogs 1–5) attained CRs after being treated with the 5-FU/epi injectable gel (mean dose of 240 mg 5-FU was delivered in a mean of 3.8 treatments). Two dogs (dogs 6 and 7) attained a PR after treatment with 5-FU/epi gel (total doses of 210 and 172 mg 5-FU in three treatments, respectively) but went on to achieve a CR after further treatment with CDDP/epi gel implants (total doses of 1.8 and 4.8 mg CDDP in three treatments). Representative SCC lesions are presented in Figures 1 and 2.

Of the six dogs that failed to achieve complete responses, three (dogs 8–10) were removed from the study at the owners' request before progression to CDDP/epi gel implants. One of these dogs subsequently was rescued surgically (dog 9). Three of the dogs that failed to attain complete response after treatment with 5-FU/epi gel were then treated with CDDP/epi gel implants (dogs 11–13). Two of these dogs subsequently were rescued by surgical resection: in dog 13 the residual necrotic tissue was excised, and in dog 11, one of the two treated sites was cured (CR), whereas the other was resected at the owner's request. The third dog that failed to attain CR after treatment with the CDDP/epi gel implant had progressive SCC (dog 12). This dog had an infiltrative, bulky tumour mass at presentation, which proved to be the largest tumour (cumulative tumour size, 102.2 cm^2) in this study. This lesion received the largest doses of both implants (834 mg of 5-FU in five implants, 40 mg of CDDP in two implants). Treatment was discontinued because the tumour progressed after the second CDDP/epi gel implant.

Tumour response expressed as dose per cumulative area of lesion treated

The five dogs that attained CR after treatment with 5-FU/epi gel implants received a mean of 102.8 ± 202.7 mg 5-FU/cm^2

cumulative tumour area, whereas the eight dogs that partially responded after 5-FU treatments received a mean dose of only 43.4 ± 45.9 mg 5-FU/cm^2 cumulative tumour area. The two dogs that attained CR after being treated with CDDP/epi gel implants received doses of 1.1 and 0.4 mg CDDP/cm^2 cumulative tumour areas, whereas the three dogs that failed to attain CR after treatment with CDDP implants received doses of 0.2, 0.4 and 0.2 mg CCDP/cm^2 cumulative tumour areas.

Patient safety evaluations

Intralesional implant therapy was well tolerated by all dogs in the study. Cutaneous reactions were limited to the treated sites. The most pronounced local skin reactions recorded were scab formation (two dogs), ulceration (seven dogs) and necrosis requiring debridement (four dogs). Lesions with complete responses healed uneventfully. None of the usual adverse effects of cytotoxic chemotherapy administration were observed and no dogs developed systemic signs of illness while under therapy with either the 5-FU/epi gel or CDDP/epi gel implants. There was no adverse effect related to the bovine collagen carrier. All dogs maintained appetites, weight and activity levels while under therapy.

Disease-free interval

Of the seven dogs that attained CR, three (dogs 3, 6 and 7) remained disease free for 60, 195 and 164 weeks, respectively, at which point they were lost to follow-up. One dog (dog 5) developed ulcerative lesions in the treated field 11 weeks after attaining CR. This was considered to be a relapse, although biopsy confirmation was not obtained. Concurrent with relapse, this dog developed generalised ulcerated calcinosis cutis secondary to hypercortisolism from a presumed pituitary microadenoma. The three remaining dogs with CR (dogs 1, 2 and 4) developed SCC lesions in different sites, but the sites treated with the therapeutic implants remained clear during the follow-up period of 345, 160 and 461 weeks, respectively. The mean disease-free interval for dogs on this study was 153 weeks (range 9–461 weeks). Of the six dogs that failed to attain complete responses after implant therapy, three (dogs 8, 10 and 12) were killed due to progressive SCC at 91, 53 and 9 weeks. Three dogs (dogs 9, 11 and 13) who had partial responses to implant therapy had residual SCC lesions that were rescued by surgery and remained alive at 90, 268 and 87 weeks.

DISCUSSION

This study demonstrates the feasibility, patient safety and efficacy of the intralesional therapeutic implants using an animal model for spontaneous sun-induced SCC. The dog represents a useful model for sun-induced SCC because the photocarcinogenesis and biological behaviour of these lesions are similar to those in human patients [1–7]. Specifically, cutaneous SCC in both species generally develop after prolonged exposure to solar radiation, and they are slow to metastasise.

The intralesional therapeutic implant delivers cytotoxic agents in a viscous colloidal gel that allows for local drug placement. Local administration of cancer drugs in this manner offers the following advantages: (1) increased concentration of drug in the tumour and (2) prolonged contact time with the drugs because of the sustained-release characteristics [8, 9, 11]. The therapeutic effect of chemotherapy is a function of adequate drug concentration and duration of exposure [15]. This modified-release intralesional delivery format increases the therapeutic index by increasing drug exposure in the tumour. Systemic toxicity is limited or absent because drug absorption in the circulation is delayed and small fractions of systemic doses are used.

The drugs 5-FU and CDDP were chosen for these studies based on their systemic efficacy in the treatment of metastatic SCC [16], cutaneous [17] and head and neck SCC [18] and canine SCC [19]. Preclinical drug retention studies in mouse tumours [8, 9], followed by clinical experience in both animal and human cancers [12–14], have supported the compatibility and efficacy of these drugs with the implant gel format. The rationale for using 5-FU as the initial treatment agent, followed by CDDP, is based on increased efficacy seen in murine studies [20].

The tumours treated in this study were given the maximum amount of therapeutic implant gel that could be physically retained by the lesions. Thus, a classical dose–response curve was not generated. However, tumours that attained a CR received average doses of 2.4 and 2.6 times as much 5-FU and CDDP per square centimetre of cumulative tumour area, respectively, than the tumours that attained a PR. The amount of implant gel that could be administered to a lesion was limited by the porosity of ulcerated tumours. Injections into ulcerated lesions were made while applying back-pressure with a sterile gauze sponge to increase retention of implant gel in the lesion. These manipulations were only partially successful. Drug may be more evenly and accurately applied by use of a grid pattern of administration. This may be pertinent for treatment of large, irregular lesions in human patients who might not be candidates for Mohs surgical procedures.

Incomplete responses due to inadequate dosing of the active chemotherapy agent may be overcome, at least in part, by increasing the number and/or frequency of injections to increase dose intensity. An intensified dose regimen with 5-FU/epi gel has been found to be efficacious in treating human basal cell carcinoma (unpublished data). Therefore, increased dosing for treatment of SCC with the implant format may be feasible without the risk of developing systemic toxicity. Standard systemic doses of 5-FU and CDDP (150 mg/m^2 and 50–70 mg/m^2 body surface area, respectively) in the dog [21], are in fact much higher than the doses delivered in the individual implant treatments in this study. It is theoretically possible to achieve 10 000 times greater drug concentrations by intralesional gel injection than by systemic administration because dose-limiting systemic toxicity is minimised and drug distribution into the target tissue is much better [11]. Thus, tumours that appear resistant to a drug administered by another route may respond when treated with intralesional implant therapy. Further, intralesional drug administration is a more efficient delivery system than topical application. The three dogs treated unsuccessfully with topical 5-FU cream before admission into this study attained CR after treatment with 5-FU/epi injectable gel implants.

In this study, intralesional therapeutic implant gels were used as "stand alone" therapy. Dogs treated had typically long-standing, refractory SCC lesions that were recurrent after a variety of conventional treatment approaches. Therefore, the 100% (13/13) PR + CR and 54% (7/13) CR rates for this group of dogs are notable. Furthermore, in three cases (dogs 9, 11 and 13) with large tumour volumes, treatment with the therapeutic implants reduced the size of the SCC enough so that they could be surgically cured. Human clinical trials of this delivery system for treating cutaneous SCC with 5-FU/epi gel and head and neck SCC with CDDP/epi gel [22] are ongoing.

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Acknowledgement—Support for this research was provided by Matrix Pharmaceutical Inc., Menlo Park, California, U.S.A.