



Jeannette M. Kelly, DVM  
Practice limited to oncology  
Veterinary Cancer Care, P.C.  
[tumorcidal@vetcancer.com](mailto:tumorcidal@vetcancer.com)  
505-982-4492(office) 505-982-1701(fax)

## Intralesional/Intraregional/Intratumoral Chemotherapy

### Definitions

Intralesional, also referred to as intraregional or intratumoral chemotherapy; is the administration of an antineoplastic drug directly into a tumor, tumor bed post surgery, and/or adjacent tissues.

### Goal

The goal is to improve local tumor control by achieving high local chemotherapeutic drug concentrations while maintaining low plasma concentrations. This results in a therapeutic gain, an increased local anti-tumor activity and decreased systemic toxicity.

### Indications

*As the primary treatment for the local control of malignant tumors:* Treatment of local disease usually involves radiation therapy or surgery. However, following these treatment modalities, a tumor that recurs is seldom successfully salvaged by reirradiation or systemic chemotherapy. (Krag et al, 1990)

*To potentiate the effects of radiation therapy:* Radiotherapy is an effective treatment for many localized solid tumors, but its curative potential can be limited by the tolerance of local normal tissues and the radiosensitivity of tumor cells. Cisplatin has been reported to enhance the cytotoxicity of radiation in vitro and in tumor bearing animals.

The mechanisms by which Cisplatin increases the cytotoxicity associated with radiation therapy are unknown. Possible mechanisms include independent cell killing or by radiosensitization; the inhibition of radiation damage repair and/or cell cycle synchronization.

*As an adjunct to surgery:* Tumor excision with wide surgical margins can sometimes be impossible if unacceptable anatomical, physiological and functional disturbances are to be avoided. The use of chemotherapeutic agents placed within the surgical wound following incomplete resection of a tumor may prolong local tumor control, aid in the achievement of a local cure or facilitate the use of techniques such as limb sparing which would otherwise be contraindicated. (Dernell et al, 1998 and Straw et al, 1994)

### Requirements

- 1) A chemotherapeutic drug that does not require systemic metabolism for conversion to its active form.
- 2) A chemotherapy drug vehicle which:
  - o Prevents rapid drug resorption
  - o Increases the time malignant cells are exposed to chemotherapeutic drugs
  - o Is biodegradable after the chemotherapeutic drug has fallen to ineffective concentrations locally
  - o Does not result in significant local toxicity
  - o Does not interfere with the action of the chemotherapy drug
  - o Allows for a controlled slow release of drug into the systemic circulation, such that high/toxic systemic drug concentrations are never achieved.

## Vehicles that have been investigated include:

### 1) A biodegradable protein carrier matrix.

This matrix is a gel made of buffered purified, sterile, non-pyrogenic bovine collagen that acts as a mechanical repository for drug, which then diffuses into the tissues. Drug retention in the tumor bed is further enhanced by the addition of epinephrine into the vehicle. This matrix is a weak immunogen and has not been associated with significant local toxicity. (Kitchell et al, 1994 and Kitchell et al, 1995)

### 2) Oily solutions

Purified sesame oil is biologically inert and non-irritating and has no cytotoxic effects. SQ injections do not result in acute or delayed inflammatory responses. It has therefore been used in the preparation of water-in-oil emulsions of chemotherapeutic drugs. When compared to aqueous solutions, purified sesame oil significantly reduces systemic exposure to Carboplatin and drug leakage from injection sites following intratumoral administration. (Theon et al, 1993 and Theon et al, 1996)

### 3) A porous solid biodegradable polymer termed Open Cell PolyLactic Acid (OPLA)

This material differs from the previous two vehicles in that it is a solid material and is therefore not injectable. Rather it is placed directly into a surgical wound following tumor excision. It is composed of a high and a low molecular weight polymer. The chemotherapeutic drug, Cisplatin is joined to the low molecular weight fraction. The final drug delivery vehicle is sterilized using gamma irradiation. Although biodegradable, this polymer persists for prolonged periods in tissues (at least 7.5 months) and is associated with a histologically detectable foreign body giant-cell reaction. This reaction and polymer persistence may be risk factors for local infection. OPLA impregnated with Cisplatin has been associated with a relatively high rate of local complications including swelling, drainage and wound dehiscence. (Straw et al, 1994 and Dernell et al, 1995 and Dernell et al, 1998)

## Side Effects

Local toxicity is the primary concern with a low risk of systemic toxicity. Side effects are rarely serious with supportive care. Patients can exhibit minor regional side effects such as swelling, redness, thinning or slow re-growth of the hair. The hair can change color and the skin can become hyperpigmented. Mild pruritis can cause the patient to rub, lick or scratch resulting in irritation, or more severe side effects such as wound formation or infection. When treating gross tumor; there is a higher chance of abscess or granuloma formation. Also, a defect can occur at the tumor site as the tumor dies. Granuloma formation can mimic tumor recurrence and a biopsy is needed for confirmation. When treating post surgical resection, there is a possibility of dehiscence of the surgery site if treating prior to complete healing. The most serious side effects are defects, tissue necrosis, wounds and infections that may need to be managed with surgical intervention. All side effects, even minor, should be managed under supervision of a veterinarian.

## Studies Using Local Chemotherapy in Clinical Small Animal Cases

**INTRALESIONAL IMPLANT FOR THE TREATMENT OF PRIMARY ORAL MALIGNANT MELANOMA IN DOGS.** Kitchell et al, JAVMA, 1994; 204:229-236

### *Tumor type*

ORAL MALIGNANT MELANOMA in 20 dogs

- o 16 dogs had advanced local disease with a bulky primary tumor > 2 cm in diameter:
- o Mean tumor volume was 7.0 (+/-1.6) cm<sup>3</sup>
- o 1 dog had pulmonary metastases
- o 5 dogs had lymph node involvement
- o 13 of the tumors were recurrent
- o Mean tumor duration prior to intralesional treatment was 20 weeks

### *Treatment protocol*

- o Implant: A protein carrier matrix (an injectable viscous gel) containing one of Cisplatin (3.3 mg/ml), Methotrexate (6 mg/ml) or Carmustine (31.3 mg/ml).
- o Treatment field: The tumor plus a 1 cm margin

- o Protocol: All tumors were treated weekly until complete tumor resolution. Cisplatin implants were used primarily. If tumors failed to decrease at least 50% in size after 3 Cisplatin treatments, Methotrexate was used. The progression to Carmustine was the same following 3 Methotrexate treatments.

### *Results*

Overall 70% (14 of 20) had a >50% decrease in tumor volume after treatment with implants.

55% of dogs (11) had a complete response (100% reduction in tumor volume)

- o Mean tumor volume = 4.13 (+/- 0.98) cm<sup>3</sup>
- o Mean total Cisplatin dose = 11.7 (+/-1.8) mg
- o Mean number of treatments = 2.6
- o One dog relapsed after 49 weeks and a complete response was achieved using the same treatment, three weeks later developed metastatic disease.
- o 2 dogs were treated with Methotrexate (total dose 27-41.6mg) and Carmustine (total dose 334-360mg) after achieving stable disease with Cisplatin

15% of dogs (3) had a partial response (>50% but <100% reduction in tumor volume)

- o Mean tumor volume = 11.74 (+/- 9.54) cm<sup>3</sup>
- o Mean total Cisplatin dose = 53.8 (+/- 26.1) mg
- o Number of treatments = 4 to 11

30% of dogs (6) had progressive disease

- o Mean initial tumor volume = 7.08 (+/- 1.89) cm<sup>3</sup>
- o All 4 tumor stages were represented

3 factors were significantly associated with favorable responses (identified by recursive partitioning):

- o Mandibular location
- o More treatments with intralesional Cisplatin
- o Consistent treatments at weekly intervals

Multiple linear regression analysis showed that the following factors were not predictive of tumor response:

- o Initial tumor stage
- o Initial tumor volume
- o Tumor duration prior to intralesional therapy
- o Prior treatment
- o Tumor cell type

Implants were well tolerated.

Systemic toxicity was minimal: renal insufficiency was not recorded

Median survival time for dogs with complete responses was 51 weeks compared to 10.5 weeks for those dogs without local tumor control.

### *Conclusion*

"The success of intralesional chemotherapy indicated that implants are a technically feasible modality for local control of oral melanomas in dogs and provide possible alternative treatment to radiation therapy or surgery."

### **INTRALESIONAL SUSTAINED-RELEASE CHEMOTHERAPY WITH THERAPEUTIC IMPLANTS FOR TREATMENT OF CANINE SUN-INDUCED SQUAMOUS CELL CARCINOMA**

Kitchell et al, European Journal of Cancer, 1995; 31A: 2093-2098

#### *Tumor type*

Primary, recurrent or refractory, measurable, histologically confirmed cutaneous SCC lesions, which were believed to be sun induced in 13 dogs. Some dogs had multiple tumors. All tumors were treated and they were considered as a single lesion with regard to response to intralesional chemotherapy. Individual tumor size was 0.2-2.94 cm<sup>2</sup> and mean cumulative tumor areas were 40.72 (+/- 37.4) cm<sup>2</sup> per dog.

#### *Treatment protocol*

- o Implant: A protein carrier matrix (gel implants that contained collagen and epinephrine) containing either 5-FU (30 mg/ml) or Cisplatin (3.3 mg/ml)

- Treatment field: tumor only
- Protocol: Weekly treatments primarily with 5-FU. If there was a <50% response with 3 treatments of 5-FU; Cisplatin was used for a minimum of 3 treatments or until complete response.

### *Results*

A mean of 5 treatments was administered to each dog. The mean cumulative dose of 5-FU was 296.7 (+/-71.5) mg (a range 75-834mg). 5 Dogs failed treatment with 5-FU and were treated with Cisplatin for a mean of 2.4 treatments and with a total cumulative dose of 13.1 (+/-8.5) mg (a range of 1.8-40mg).

- 7/13 (54%) had complete resolution with 5-FU or Cisplatin
- 6/13 (46%) had at least 50% reduction in cumulative tumor area (3 of these dogs were removed from the study prior to progression to Cisplatin)
- The five dogs that achieved complete remission with Cisplatin alone received a mean of 102.8 (+/- 202.7) mg 5-FU/cm<sup>2</sup> cumulative tumor area, whereas the 8 dogs that failed to achieve a complete remission with Cisplatin only received 43.4 (+/- 45.9) mg 5-FU/cm<sup>2</sup> cumulative tumor area
- Local tissue reactions included: scab formation (2), ulceration (7), and necrosis requiring debridement (4). All local reactions healed uneventfully
- No systemic toxicity occurred
- Disease free interval was difficult to assess as dogs were lost to follow up, but ranged from 11 days to 461 days. However this disease free interval does not take into consideration the appearance of SCC at new sites.

### *Conclusion*

"Sustained release chemotherapy using intralesional 5-FU/epi gel and Cisplatin (CDDP)/epi gel therapeutic implants is effective in treating canine sun-induced SCC of the skin."

## **INTRATUMORAL ADMINISTRATION OF CARBOPLATIN FOR TREATMENT OF SQUAMOUS CELL CARCINOMAS OF THE NASAL PLANE IN CATS**

Theon et al, AJVR, 1996; 57: 205-209

### *Tumor type*

23 Cats with Squamous Cell Carcinoma of the nasal plane.

### *Treatment protocol*

- 8 cats received 100mg of Carboplatin/m<sup>2</sup> of body surface area intratumoral with or without purified sesame oil over four weekly treatments using a 2-period cross over design
- 15 cats received intratumoral administration of Carboplatin in purified sesame oil. Each of these cats received 4 weekly treatments at a dosage of 1.5mg/cm<sup>2</sup> tissue

### *Results*

- 67% had complete clinical tumor clearance within the treatment period
- 73.3% had a complete clinical response defined as complete disappearance of the tumor for a minimum of 4 weeks
- Mean progression free survival was 16 (+/- 3.3) months
- The one year progression free survival rate was 55.1 (+/- 13) %
- Local recurrence was observed in 7 cats: 4 had marginal tumor recurrence and 3 had both the latter and in-field recurrence
- Systemic toxicity was not observed
- Local toxicity was minimal and resolved after treatment

### *Conclusion*

"Intratatumoral administration of Carboplatin in a water-sesame-oil emulsion was found to be a practical and effective new treatment for facial squamous cell carcinomas in cats."

## **THE EFFECT OF INTRALESIONAL BLEOMYCIN ON CANINE ACANTHOMATOUS EPULIS**

Yochida et al, 1998, J Am Anim Hosp Assoc; 34: 457-461

### *Tumor type*

4 Dogs with recurrent Acanthomatous Epulis

### *Treatment protocol*

Weekly intralesional injections of 5 mg Bleomycin. No drug vehicle was used.

### *Results*

- 3 dogs received 8 to 10 injections. Complete tumor remission was noted in all dogs for the duration of the follow up periods, which ranged from 1 to 2 years.
- Ulceration was noted in one dog, but resolved.
- The fourth dog received 6 injections, which resulted in a partial response, but treatment was discontinued by the owner and the dog was lost to follow up.
- No systemic toxicity was noted.
- Immunohistochemical staining showed a decrease in the number of cells in the G1, G2 and M phases of the cell cycle at the tumor site.

### *Conclusion*

"Intralesional Bleomycin may be an effective treatment for the local control of Acanthomatous Epulis. Bleomycin may be effective by inhibiting DNA synthesis in tumor cells."

## **INTRACAVITARY TREATMENT OF SOFT TISSUE SARCOMAS IN DOGS USING CISPLATIN IN A BIODEGRADABLE POLYMER**

Dernell et al, Anticancer Research, 1997; 17: 4499-4506

### *Tumor type*

- 32 Soft Tissue Sarcomas in 30 dogs
- Median tumor diameter was 3 cm (range 1-14cm)

### *Treatment protocol*

- The tumors were resected with histologically dirty margins
- A Cisplatin impregnated OPLA implant ( a porous body composed of a biodegradable polymer) was implanted within the surgical site at the time of or within 30days of incomplete resection
- Median Cisplatin dose was 34.5 mg/m<sup>2</sup> total body area (range 5.3-133.3mg/m<sup>2</sup>)

### *Results*

- Median follow-up time 335days with a range of 113-1580 days
- 31% recurrence rate
- Median time to recurrence was greater than 640 days (range 30-640 days) and was not defined by time life analysis
- Median time to metastasis was 978 days (range 100-978 days)
- Median survival was 1021 days (range 44-1021 days)
- High tumor grade had a significant (p=0.031) negative effect on local recurrence
- Significant local side effects were noted: swelling 19/32 (60%) and OPLA-Pt removal in 9/32 (28%), median time to removal was 13 days (range 6-67days)

### *Conclusion*

"Rate of recurrence appeared to be similar using intracavitary Cisplatin compared to previous reports of STS treated by marginal surgery followed by radiotherapy. The complication rate indicates the need for further refinement of the polymer/Cisplatin system."

## REFERENCES

- Dernell et al 1997. Intracavitary treatment of soft tissue sarcomas in dogs using Cisplatin in a biodegradable polymer. *Anticancer Research*; 17: 4499-4506
- Kitchell et al 1994. Intralesional implant for the treatment of primary oral malignant melanoma in dogs. *JAVMA*; 204: 229-236
- Kitchell et al 1995. Intralesional sustained-release chemotherapy with therapeutic implants for treatment of canine sun-induced squamous cell carcinoma. *European Journal of Cancer*; 31A 2093-2098
- Krag et al 1990. Intralesional Cis-Diamminedichloroplatinum and purified collagen treatment of human metastatic malignancies. A feasibility study. *Journal of Surgical Oncology*; 43: 83-87
- Straw et al 1994. Effects of Diamminedichloroplatinum II released from D, L-Polyactic acid implanted adjacent to cortical allografts in Dogs. *J Orthop Res*; 12: 871-877
- Theon et al 1994. Concurrent Irradiation and Intratumoral Chemotherapy With Cisplatin: A Pilot Study In Dogs With Spontaneous Tumors. *Int J Radiation Oncol Biol Phys*; 29: 1027-1034
- Theon et al 1996. Intratumoral administration of Carboplatin for treatment of squamous cell Carcinomas of the nasal plane in cats. *AJVR*; 57: 205-209
- Yoshida et al 1998. The effect of intralesional Bleomycin on canine acanthomatous epulis. *J Am Anim Hosp Assoc*; 34: 457-461