Inhalation Chemotherapy for Macroscopic Primary or Metastatic Lung Tumors: Proof of Principle Using Dogs with Spontaneously Occurring Tumors as a Model

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ABSTRACT

This study represents part of an effort to determine the safety and efficacy of inhaled antineoplastic drugs, using pet dogs with spontaneously arising primary and metastatic lung cancers (including sarcoma, carcinoma, and malignant melanoma) as a model. Dogs received new formulations of either paclitaxel (PTX) or doxorubicin (DOX) by the inhalation route every 2 weeks using a specially designed aerosol device. Response was assessed radiographically using the indices of tumor nodule number and volume measurement of discrete pulmonary nodules. Dogs experiencing progressive disease after two consecutive treatments were crossed over to receive the alternate compound. In 24 dogs, 6 (25%) responses were noted including 5 partial responses (PR) and 1 complete response. These include 4 (22.2%) of 18 responses to DOX and 2 (13.3%) of 15 responses to PTX. Responses were noted with osteosarcoma (including three dogs with metastatic osteosarcoma that had failed prior systemic chemotherapy), liposarcoma, hemangiosarcoma, and undifferentiated sarcoma. One dog with mammary carcinoma experienced a 47% reduction in volume after PTX inhalation, just shy of PR criteria. One dog with liposarcoma is experiencing a long-term (>12 months) stabilization of disease on PTX. To date, no systemic toxicities have been observed with either PTX or DOX inhalations. Local (pulmonary) toxicity was not observed with PTX; however, changes consistent with pneumonitis/fibrosis were observed in some dogs receiving DOX. Only one of these dogs showed clinical signs, which were responsive to steroid and antitusive therapy. These data represent “proof of principle” for the avoidance of systemic toxicity while delivering efficacious local drug levels by the inhalation route.

INTRODUCTION

The administration of drugs directly to the lungs via inhalation offers several potential advantages over oral and parenteral administration. These include the extensive pulmonary surface area available for drug absorption, the avoidance of first pass metabolic degradation by the liver and/or intestines, and the noninvasive nature of administration (1). Inhalation also offers the possibility of locoregional drug delivery to the lungs and airways with smaller doses and fewer systemic effects (2, 3). Inhalational delivery has been used primarily for airway diseases. The most common application of aerosol technology is the delivery of bronchodilators and corticosteroids by inhalation for bronchial asthma. Increasing evidence now exists to support the role of inhaled therapeutics in the treatment of parenchymal lung diseases. Examples include the use of nebulized aminoglycoside antibiotics for respiratory infections in patients with cystic fibrosis or those undergoing mechanical ventilation (4–9), pentamidine for the prevention of pneumocystis carinii infection in patients with HIV (10–12), and antiviral agents for the treatment of human respiratory syncytial virus and influenza virus (13–16). Additionally, aerosolized cyclosporine is undergoing evaluation for the treatment of allograft rejection in patients receiving lung transplants (17, 18). However, the concept of delivering chemotherapeutics by inhalation for the treatment of lung cancer, either primary or metastatic, has received little attention.

The outcome for the treatment of primary and metastatic lung cancer in humans has not changed dramatically despite the availability of new chemotherapeutic agents. The reasons for treatment failure are diverse, but one possibility may be the inability to deliver adequate drug concentrations to the tumor site with systemic administration. Pulmonary delivery of antineoplastic drugs offers the theoretical advantage of achieving high local pulmonary concentrations of a drug while minimizing systemic exposure. Thus the possibility exists of optimizing local action of chemotherapeutics with significantly lower overall dose and fewer systemic side effects. The efficacy of locoregional application of chemotherapy has been demonstrated in a variety of cancers including liver, bladder, and ovarian cancer. Isolated lung perfusion has been used with limited success in a small number of patients (19) but is unlikely to be widely used because it requires surgery.

Few studies exist documenting the feasibility of delivering antineoplastic agents by inhalation. Tatsumura et al. (20) eval-
Inhalation chemotherapy for lung cancer is a targeted approach that delivers chemotherapeutic compounds by the inhalation route. In this study, aerosolized liposomal interleukin 2 has been demonstrated to induce objective regressions in normal dogs, and when administered to dogs with spontaneously occurring lung tumors, objective regressions were observed.

There is no documented clinical experience to date of DOX or PTX locoregional delivery to the lungs via inhalation for lung tumors. Preclinical studies, performed by the authors in normal rodents and dogs, have demonstrated the feasibility of delivering chemotherapeutic compounds by the inhalation route without serious toxicity. This study represents part of an effort to determine the safety and efficacy of pulmonary-delivered anti-neoplastic drugs, using pet dogs with spontaneously arising primary and metastatic lung cancers.

SUBJECTS AND METHODS

Subject Population. Twenty-eight privately owned dogs with spontaneously occurring primary or metastatic lung tumors presenting to the University of Wisconsin Veterinary Medical Teaching Hospital (UW-VMTH) between August 1997 and August 1998 were treated. Pretreatment evaluation included complete physical examination, complete blood cell count with platelet count, biochemistry profile, urinalysis, thoracic radiographs, modified Karnofsky performance score (24), and histopathological assessment of tumor type. Dogs with gross, measurable primary or metastatic lung cancers, including sarcomas, carcinomas, and malignant melanomas were eligible for study. Eligible dogs were free of complicating concurrent disease, had adequate hematological and serum biochemical parameters to undergo chemotherapy, and had a modified Karnofsky score of 2 or lower. For dogs with metastatic lung cancer, the primary extra-thoracic tumor was managed previously or concurrently. If the patient’s primary extra-thoracic tumor required concurrent therapy, such therapy was of a local modality only (surgery and/or local radiotherapy). Informed consent and agreement to necropsy forms were signed by each dog’s owner before entry.

Treatment. Dogs received newly developed inhalation solutions of either PTX or DOX by inhalation once every 2 weeks. DOX HCI was purchased from Alfa Aesar (Ward Hill, MA), and was dissolved in 20% ethanol at a concentration of 16 mg/ml. PTX was purchased from Hande Tech, (Houston, TX) and was dissolved in a mixture of polyethylene glycol 200 and ethanol at 75 mg/ml. An aerosol device especially designed to capture all of the exhaled and fugitive drug was used (Fig. 1). The device consists of a Pari LC Jet nebulizer, an aerosol plenum, an intake and an exhaust filter contained within a sealed ABS/polycarbonate box maintained under negative pressure to prevent escape of fugitive aerosol. Additionally, all of the exhaled air is routed through the exhaust filter. It has been demonstrated in laboratory studies that no detectable drug passed through the filter during the operation of the device. Further verification of the trapping efficiency of the filter was performed by nebulizing Tc 99m-spiked vehicles. Initially, the study was conceived to involve randomization into one of the two treatment groups with cross-over to the alternate compound, should treatment fail. However, because of the initial unavailability of PTX, the majority of dogs were started on DOX therapy. Dogs were anesthetized with an i.v. bolus of propofol and were maintained on a continuous rate infusion. The goal was to maintain a light plane of anesthesia that allowed for spontaneous respirations. Inhalation compounds were delivered to the patient by use of an endotracheal tube. Oxygen was supplemented at 100% to all of the dogs with each event. The targeted dose delivery to the pulmonary tree was 3 mg of DOX and 40 mg of PTX per inhalation therapy event. The doses used in this study were selected on the basis of results obtained in normal beagle dogs. In those studies, inhalational DOX was given to groups of six dogs per sex at doses ranging from 1 to 10 mg/m² BSA (total deposited dose) and of PTX ranging from 10 to 90 mg/m². Doses of DOX greater than 3 mg/m² deposited in the respiratory tract caused severe local toxicity. By contrast, inhaled PTX caused little or no local toxicity but, at the highest dose, did cause about a 50% decrease in the WBC count. Thus, pulmonary deposition of 3 mg and 40 mg, DOX and PTX, respectively, assuming a BSA of one square meter, were selected for the present study. The amount of each drug delivered was controlled by the duration (in minutes) of inhalation exposure. This was calculated based on the dog’s stabilized minute-volume of respiration under light anesthesia and ranged from 5 to 21 min. Heart rate, respiratory rate, and oxygen saturation were monitored during each event. When possible, a sample of blood was collected from either the lateral saphenous or the jugular vein before, and up to 20 min after, exposure, for an assay of plasma drug levels.

A total of six biweekly therapies were scheduled per patient unless additional therapy was warranted based on continued response. If a dog failed to achieve a response after two consecutive treatments with a particular agent, cross-over to the alternate compound was offered. Dogs were withdrawn from the study if they failed to achieve a response after the completion of cross-over therapy, the modified Karnofsky performance score declined to 3 or higher, a clinical or clinicopathological abnormality occurred that precluded safe continuation of inhalant therapy, or the owner requested the dog be dropped from the study.

Response. Thoracic radiographs were performed before each treatment event to assess the response. Radiographic interpretation included quantitative measurements of tumor nodule number and volume (V = 4/3πr³) of discrete pulmonary nodules performed by a single, board-certified veterinary radiologist. The end point of study was response to therapy. Response to therapy was categorized as CR (complete regression of all of the measurable tumors); PR (greater than 50% decrease in volume of all of the measurable tumors); stable disease (less than a 50% decrease or no more than a 25% increase in the volume of all of the measurable tumors); or progressive disease.
(a 25% or more increase in tumor volume or the appearance of new lesions). CR and PR were the only responses considered.

**Toxicity.** At each evaluation and treatment, dogs received a complete physical examination, complete blood cell count, biochemistry profile, and urinalysis and were assigned a modified Karnofsky Performance Score. Any changes in hematological or serum biochemical parameters or performance status compared with pretreatment evaluation, as well as any clinical adverse effects, were noted.

**RESULTS**

**Subject Demographics.** Twenty-eight dogs were entered into study. Ages ranged from 1.5 years to 16 years (median, 10 years). There were 13 neutered males, 11 spayed females, 2 intact males, and 2 intact females. Body weights ranged from 12.6 to 51.6 kg (mean, 31.9 kg; median, 32 kg). Tumor histologies included OSA (n = 10), bronchogenic carcinoma (n = 3), hemangiosarcoma (n = 3), mammary carcinoma (n = 3), thyroid carcinoma (n = 2), and one each of squamous cell carcinoma, chondrosarcoma, rectal adenocarcinoma, fibrosarcoma, undifferentiated sarcoma, malignant melanoma, and liposarcoma. Eleven breeds were represented, including 11 Labrador retrievers (5 with OSA and 1 each with liposarcoma, rectal adenocarcinoma, bronchogenic carcinoma, thyroid carcinoma, and mammary carcinoma), 4 German shepherds (2 with hemangiosarcoma and 1 each with melanoma and squamous cell carcinoma), 3 doberman pincers (2 with OSA and 1 with undifferentiated sarcoma), 2 rottweilers (1 with OSA and 1 with chondrosarcoma), 2 mix breeds (1 with bronchogenic carcinoma and 1 with thyroid carcinoma), and 1 each of Siberian husky (bronchogenic carcinoma), golden retriever (fibrosarcoma), Australian shepherd (mammary carcinoma), English pointer (OSA), Samoyed (OSA), and Akita (mammary carcinoma). Thirteen dogs received both DOX and PTX in a cross-over setting, 9 dogs received DOX only and 6 dogs received PTX only. At the time of writing, 25 dogs have died because of disease (4 died before an evaluation of response), and 3 dogs are still alive. Tissues were available for postmortem examination in all but one case.

**Plasma Drug Levels.** Pre- and posttreatment blood samples were obtained from 18 dogs exposed to DOX and 16 dogs exposed to PTX. Both drugs were present in plasma samples taken within 1 min after inhalation of the drug, with concentrations falling rapidly over the next several minutes. Because serial blood samples were not collected from each dog and because the dogs were not dosed on the basis of body weight or body surface area, no pharmacokinetic analyses were possible. The concentrations of drug in plasma ranged from 0.5 to 10 ng/ml for DOX and from 175 to 1245 ng/ml for PTX. These levels are less than one-tenth of the maximum concentrations of these drugs in plasma from normal dogs after i.v. administration of 20 mg/m² and 160 mg/m² DOX and PTX, respectively, doses in the therapeutic range for these drugs in dogs (25).

**Response.** Evaluation of response was available in 24 cases. A total of six responses—five PR and one CR—were observed for an overall response rate of 25%. This included 4...
(22.2%) of 18 evaluated DOX-treated dogs (all PR) and 2 (13.3%) of 15 evaluated PTX-treated dogs (1 PR, 1 CR). Figs. 2 and 3 represent examples of tumor responses to inhalation therapy. Tumor types experiencing responses include OSA (n = 3) and one each of liposarcoma, hemangiosarcoma, and undifferentiated sarcoma. One dog with mammary carcinoma experienced a 47% reduction in volume after PTX inhalation, just shy of PR criteria. Durations of response ranged from 14 to ≥324 days (median, 28 days). Additionally, one dog with widespread metastatic liposarcoma is presently experiencing a long-term stabilization of disease on PTX inhalation (>495 days) after initially failing DOX inhalation therapy.

**Toxicity.** No systemic chemotherapy-related toxicities, either measurable or dose-limiting, (including cardiotoxicity) were observed with either PTX or DOX inhalations. Hematological and serum biochemical parameters before, and 2 weeks after, inhalation therapy are presented in Table 1. Local (pulmonary) toxicity was not observed clinically with PTX therapy.
nor was there histological evidence of pathology on necropsy tissues; however, approximately one-half of the dogs receiving DOX inhalation developed an intermittent, nonproductive cough within 1–10 days of therapy. This cough was typically self-limiting and was not dose-limiting in any animal. Clinical signs were severe enough in only three dogs to warrant short-term antitussive therapy. No client withdrew their animal from therapy in any case. Histological changes consistent with DOX-associated cardiotoxicity were evident in two dogs receiving DOX by the inhalation route. However, the changes were described as chronic in nature and both dogs had received four courses of systemic DOX (30 mg/m² i.v. every 3 weeks) as part of their original OSA therapy before entering this trial with recently developed pulmonary metastasis. The dogs that received DOX by the inhaled route had histological changes consistent with the following conditions: (a) mild-to-moderate toxic-induced pneumonitis (n = 8); (b) mild-to-moderate multifocal interstitial fibrosis (n = 5); (c) mild alveolar histiocytosis (n = 3); and (d) mild-to-moderate type II pneumocyte proliferation (n = 3). None of these dogs had accompanying clinical or radiographic signs of pneumonitis or pulmonary fibrosis.

**DISCUSSION**

One difficulty in the treatment of lung cancers, whether primary or metastatic, is the inability to deliver adequate concentrations of drug to the tumor, without serious adverse systemic effects. This study has demonstrated a safe and effective means of locoregional delivery of chemotherapy to the lungs. Tumor regression was achieved in 25% of the dogs with measurable lung tumors that received biweekly treatments of inhaled formulations of DOX or PTX. Additionally, the delivery of efficacious doses of PTX and DOX did not result in side effects normally associated with systemic administration of these drugs. It is important to bear in mind that the majority of dogs enrolled in this study presented with advanced stages of primary or metastatic cancer. Many of these dogs had been pretreated with chemotherapy, and the majority had failed standard treatment protocols. Therefore, cures and durable responses were not a reasonable expectation.

Three of the six responders were dogs with pulmonary metastatic OSA. Two dogs achieved partial remissions with DOX inhalation, and one dog demonstrated partial regression of metastatic hilar lymphadenopathy, which suggested uptake of the inhaled drug into regional lymph nodes. Similar observations have been made by Tatsumura et al. (20), who demonstrated high concentrations of 5-FU in hilar lymph nodes in dogs undergoing inhaled administration of the drug. Similarly, exposure of the lung to DOX by isolated perfusion was capable of achieving significantly higher drug levels in lymph nodes and lung (19, 26).

The CR occurred in a dog with a solitary OSA metastasis. This dog demonstrated complete regression of tumor after three PTX inhalation treatments. Four additional treatments were administered after the CR, and the dog remains disease-free at the time of writing (>325 days). These responses in dogs with OSA are particularly noteworthy for two reasons: (a) systemic chemotherapy is virtually ineffective for canine OSA once gross pulmonary metastases develop (27). Only 1 PR, lasting 21 days, occurred in 45 dogs undergoing single-agent systemic chemotherapy for pulmonary metastatic disease (27); and (b) all of the three dogs with OSA that exhibited responses to inhaled drug had received prior systemic chemotherapy. Two of them demonstrated responses to inhaled DOX after having received systemic DOX before the development of their pulmonary metastases.

Of eight evaluable dogs with a carcinoma, only one (mammary) achieved a near response (47% reduction in volume). Most dogs undergoing inhalation therapy for carcinomas had advanced primary lung or metastatic mammary cancers. Although, historically, carcinomas respond more favorably to systemic chemotherapy than sarcomas, the lack of response of carcinomas in this study may be by virtue of extensive tumor burden rather than tumor type. This may reflect an inability to achieve adequate drug penetration into larger tumors. This is supported by the observation in several of our dogs that within the same patient, small nodules often regressed, whereas larger

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-DOX (±SD)</th>
<th>Post-DOX (±SD)</th>
<th>Pre-PTX (±SD)</th>
<th>Post-PTX (±SD)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils (/μl)</td>
<td>8,883 (4,434)</td>
<td>8,616 (5,154)</td>
<td>8,043 (3,412)</td>
<td>10,150 (5,696)</td>
<td>3000–12,000</td>
</tr>
<tr>
<td>Platelets (× 1000/μl)</td>
<td>306 (168)</td>
<td>320 (95)</td>
<td>271 (73)</td>
<td>272 (82)</td>
<td>200–500</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>10.8 (0.4)</td>
<td>10.7 (0.4)</td>
<td>10.8 (0.4)</td>
<td>10.5 (0.4)</td>
<td>9.5–11.2</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>4.3 (0.5)</td>
<td>4.5 (0.7)</td>
<td>4.6 (0.7)</td>
<td>4.3 (1.0)</td>
<td>2.6–6.2</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>99 (16)</td>
<td>98 (15)</td>
<td>98 (9)</td>
<td>98 (11)</td>
<td>66–119</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>12 (3)</td>
<td>12 (2)</td>
<td>14 (6)</td>
<td>11 (2)</td>
<td>8–25</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.0 (0.2)</td>
<td>1.0 (0.2)</td>
<td>1.0 (0.2)</td>
<td>0.9 (0.9)</td>
<td>0.7–1.5</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>6.3 (0.4)</td>
<td>6.1 (0.3)</td>
<td>6.4 (0.4)</td>
<td>6.2 (0.5)</td>
<td>4.5–7.6</td>
</tr>
<tr>
<td>ALK-P (units/liter)</td>
<td>3.2 (0.4)</td>
<td>3.1 (0.3)</td>
<td>3.3 (0.2)</td>
<td>3.2 (0.4)</td>
<td>2.5–4.0</td>
</tr>
<tr>
<td>ALK-P (units/liter)</td>
<td>183 (172)</td>
<td>209 (197)</td>
<td>237 (308)</td>
<td>240 (270)</td>
<td>0–166</td>
</tr>
<tr>
<td>Creatine kinase (units/liter)</td>
<td>247 (234)</td>
<td>202 (163)</td>
<td>113 (82)</td>
<td>335 (377)</td>
<td>7–203</td>
</tr>
<tr>
<td>AST (units/liter)</td>
<td>43 (17)</td>
<td>43 (20)</td>
<td>39 (18)</td>
<td>42 (22)</td>
<td>0–44</td>
</tr>
<tr>
<td>ALT (units/liter)</td>
<td>47 (39)</td>
<td>44 (27)</td>
<td>60 (44)</td>
<td>48 (33)</td>
<td>0–79</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>236 (69)</td>
<td>237 (64)</td>
<td>250 (89)</td>
<td>257 (71)</td>
<td>111–290</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>236 (88)</td>
<td>237 (64)</td>
<td>250 (89)</td>
<td>257 (71)</td>
<td>111–290</td>
</tr>
</tbody>
</table>

* BUN, blood urea nitrogen; ALKP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
nODULES remained static or progressed. We currently are completing a study in dogs with spontaneous primary lung carcinomas after lobectomy to resect gross parenchymal disease whose hilar regional nodes are determined to be positive histologically for metastasis. These dogs are receiving inhalation chemotherapy after cytoreductive lobectomy and will represent a mode for efficacy in the micrometastatic setting rather than the macroscopic setting used in the present study.

No dog that achieved an initial response with one drug achieved a response when crossed-over to the alternate compound. However, one dog with liposarcoma metastases that progressed on DOX has had a long-term stabilization of disease (>495 days) with PTX inhalation therapy. It appears that the inhaled PTX has resulted in the inhibition of tumor growth, perhaps by the known antiangiogenic effects of PTX. Remarkably, this dog has a considerable tumor burden but remains asymptomatic and leads a normal life.

Administered doses of drugs were sufficient to result in regression of tumors without associated toxicity. The acute side effects of myelosuppression, nausea, and vomiting frequently associated with i.v. administration of PTX and DOX were not observed in any dog. Cardiotoxicity, a cumulative dose-liming effect of i.v. administration of DOX, was not observed in any dog receiving DOX inhalation alone. These findings are consistent with the results of distribution of 14C-DOX after i.v. or inhalation administration in normal beagle dogs (28). Levels of 14C in lung were demonstrated to be 15–20 times higher after inhalation administration in normal beagles revealed that all of the three dogs received more than 5 mg/m² deposited dose, well above the maximum tolerated dose for single exposure of DOX of 1.3 mg/m² for chronic pulmonary changes in normal beagle dogs (data not shown).

No attempt was made in this trial to optimize the dosing procedure. The alternate-week dosing schedule was based on the cyclic dosing of cytotoxic drugs given i.v. in which myelosuppression is generally dose-limiting. However, for inhalational chemotherapy, in which local or regional responses are desired and local toxicity may be dose-limiting, a schedule based on nonpulmonary drug effects may not be appropriate. Studies to determine the most effective dose and schedule for each drug, together with a pharmacokinetic evaluation, will be important for the future development of this treatment modality. Although there was no indication of bronchospasm in these dogs, it is conceivable that pretreatment with a bronchodilator may improve the distribution of the aerosolized drug within the lung and improve its efficacy in some dogs. Thus, although there seems to be ways by which the effectiveness of inhaled chemotherapy can be enhanced, the results of this trial support the role of inhalational chemotherapy as targeted local therapy in the treatment of primary and metastatic lung cancers. Responses were achieved in several animals that had previously undergone and failed standard systemic chemotherapy protocols. The doses of inhaled agents that resulted in responses were well tolerated in all of the animals, with minimal-to-no side effects. This trial also demonstrates the utility of spontaneous tumors in animals as translational models for the evaluation of these and other novel anticancer therapies.

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REFERENCES

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