Intratumoral Administration of Cisplatin for Treatment of Sarcoids in 378 Horses

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Intratumoral chemotherapy with cisplatin is a practical, effective, and inexpensive method of treatment for equine sarcoids. Treatment resulted in no cosmetic or functional deficits. Factors that negatively affected treatment efficacy included larger tumor size and prior use of other treatment modalities. Authors’ addresses: Department of Surgery and Radiology (Théon, Galuppo, Snyder) and Department of Medicine and Epidemiology (Wilson), School of Veterinary Medicine, University of California, Davis, CA 95616; e-mail: aptheon@ucdavis.edu. © 2006 AAEP.

1. Introduction

The efficacy of intratumoral chemotherapy with cisplatin for equine cutaneous tumors has been described in several reports with relatively small numbers of patients. The goals of this study were to analyze the efficacy and toxicity of intratumoral chemotherapy with cisplatin in a large group of horses with sarcoids and to determine prognostic factors influencing response to treatment and toxicity.

2. Materials and Methods

Animals

Three hundred sixty-eight horses with 409 histologically confirmed sarcoids and a minimum of 3-yr follow-up after treatment at University of California, Davis-Veterinary Medical Teaching Hospital (UCD-VMTH) were entered in this study. Mean and median ages were 9 and 10 yr, respectively. Tumor locations included the periorbital region (58%), face and ear pinnae (11%), trunk and neck (10%), limbs (17%), and male genital area (4%). Staging was done by use of the tumor/node/metastasis (TNM) classification system in which the T category indicated maximum diameter of tumors (microscopic disease = T0; <2 cm = T1; 2–5 cm = T2; 5–10 cm = T3; >10 cm = T4). Tumor stages included T0 (13%), T2 (63%), T3 (19%), and T4 (5%). Various alternative treatments had been attempted on 91 horses, 4–9 mo before treatment with cisplatin.

Treatment Procedures

Treatment included a series of four intratumoral administrations of cisplatin given at 2-wk intervals. Cisplatin was formulated in a water–sesame oil emulsion for intratumoral administration as described elsewhere. Dosages were 1 mg of cisplatin (i.e., 0.3 ml of mixture) for each cubic centimeter of tissue in the target field (tumor bed and a margin of normal tissue). Seventy-four lesions were treated with cisplatin alone, and 335 were treated with cisplatin in combination with surgery. When treatment was combined with surgery, cisplatin was administered either after incomplete resection de-
defined by histological examination of surgical margins (N = 52), after grossly incomplete resection without wound closure (N = 47), or with primary closure (N = 246). Intratumoral chemotherapy was started at the time of surgery (N = 146) or 2–3 wk post-operatively when wound healing was complete (N = 199). Drug handling and administration and aftercare of the horses were as previously described.4

Data Analysis

Duration of post-accrual follow-up monitoring ranged from 37 to 69 mo (median, 47 mo). Endpoint for treatment efficacy was local control of the tumor. Duration of local control was defined as the interval elapsed between the end of treatment and tumor recurrence. Local control rates were estimated by use of the product-limit method.5 Recurrence included tumor regrowth in the treated field (in-field recurrence) or at the margin of the treated field (marginal relapse). Variables examined as indicators of prognosis included tumor appearance (verrucous, fibroblastic), tumor size before treatment, tumor size before cisplatin treatment, wound closure, tumor location, cumulative dose of cisplatin, treatment delay, and previous treatments. The Cox proportional hazards regression model was used to identify significant prognostic factors of local tumor control.6 Differences were considered significant at p < 0.05. Treatment complications were assessed on the basis of severity of normal tissue reactions. Reactions observed in normal surrounding tissue during the course of treatment were graded as grade 1 (tenderness with slight edema), grade 2 (moderate edema lasting <3 days and focal crusting), and grade 3 (moderate edema lasting >3 days, patchy crusting). Logistic regression analyses were used to assess the independent effect of the variables on risk and severity of skin reactions.7

3. Results

All horses completed the planned four treatment sessions. Mean dose per treatment session was 0.97 ± 0.23 (SEM) mg cisplatin/cm³ of tumor tissue treated. Doses tended to be higher for smaller tumors and lower for larger tumors. Cumulative dose of cisplatin injected ranged between 20 and 168 mg.

The overall 3-yr local control rate was 97 ± 2% (SE). The 3-yr local control rates according to treatment protocol and tumor stage are given in Table 1. Treatment failure was histologically confirmed in 11 lesions (7 marginal recurrences and 4 in-field recurrences). Prognostic factors significantly affecting local control were tumor stage before cisplatin treatment (p = 0.003) and previous treatment (p = 0.001). Treatment efficacy was lower for large tumors, those with gross postoperative residual disease and those that had been treated previously with other modalities.

Severity of reactions observed in tissue surrounding tumors ranged from grade 1 to 3 (Fig. 1). Skin reactions were self-limiting and resolved quickly. All reactions healed within 4 wk of treatment completion without scarring, skin depigmentation, and hair color change or hair loss. Treatment did not compromise the healing of open or closed surgical wounds. Drug-related systemic toxicity or hypersensitivity reactions were not observed. Treatment was used safely on four pregnant mares and six stallions. In some patients, phenylbutazone or flunixin meglumine was prescribed for 5 days after

### Table 1. Local Control Rates in 378 Horses With 409 Sarcoids Treated By Intratumoral Chemotherapy With Cisplatin Alone or in Combination With Surgery

<table>
<thead>
<tr>
<th>Treatment procedure</th>
<th>Stage (N Horses)</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>3-yr Local Control Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin alone</td>
<td>—</td>
<td>24</td>
<td>32</td>
<td>8</td>
<td>—</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Perioperative cisplatin, open wound, gross residual disease</td>
<td>—</td>
<td>—</td>
<td>7</td>
<td>17</td>
<td>23</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>Perioperative cisplatin, closed wound, gross residual disease</td>
<td>—</td>
<td>—</td>
<td>63</td>
<td>36</td>
<td>—</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>Postoperative cisplatin, closed wound, gross residual disease</td>
<td>—</td>
<td>—</td>
<td>49</td>
<td>77</td>
<td>21</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>Postoperative cisplatin, closed wound, microscopic residual disease</td>
<td>52</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Risk of skin reaction from intratumoral chemotherapy with cisplatin after each treatment session. Skin reactions were categorized as grade 1 (tenderness with slight edema), grade 2 (moderate edema lasting <3 days and focal crusting), and grade 3 (moderate edema lasting >3 days, patchy crusting).
treatment as needed to minimize inflammation at the site of injection. Fourteen horses had a treatment session delayed for 1 wk between the third and fourth administration because of acute skin reaction (grade 3). The risk of developing a grade 3 skin reaction was higher in horses treated previously with cryotherapy ($p = 0.02$) or use of caustic ointments ($p = 0.001$). The severity of skin reactions was significantly associated with treatment number ($p < 0.001$) and cumulative dose of cisplatin ($p = 0.04$).

4. Discussion

This study confirms the efficacy of intratumoral chemotherapy with cisplatin for equine sarcoids. Treatment efficacy was not affected by the clinical appearance or location of the tumor. When combined with surgery, optimal results were obtained after gross resection of the tumor leaving only microscopic or minimal residual tumor. The optimal timing of the two treatment modalities depends on several factors including tumor location, extent of surgical resection, type of surgical wound, and volume of residual tumor. Intratumoral chemotherapy should be started at the time of surgery when primary closure is not possible. After incomplete removal of gross tumor when the risk of post-operative complications is low, intratumoral chemotherapy may be started at the time of surgery. After extensive tumor resection, when there is a high risk of surgical morbidity and wound dehiscence or after microscopically incomplete surgical resection, intratumoral chemotherapy should be initiated after complete skin healing (10–14 days post-operatively). The delay between incomplete excision and chemotherapy should be kept as short as possible to minimize the negative effects of active tumor regrowth.8

Local control rate at 3 yr after treatment was found to be an accurate estimate of the cure rate. The risk of tumor recurrence after 3 yr was negligible. This emphasizes the need for long-term follow-up to assess antineoplastic treatments in horses. Prognostic factors significantly affecting local control were tumor size before cisplatin treat-ment and previous unsuccessful treatment. Large tumors and tumors that recurred after treatment other than intratumoral cisplatin were less likely to respond to treatment. This emphasizes the need to treat equine sarcoïds early and adequately.

Treatment was safe and resulted in excellent cosmetic and functional results. Drug-related systemic toxicity has not been observed. Treatment-associated skin reactions resolved quickly with no evidence of permanent cosmetic or functional deficit. Treatment of grossly infected lesions was associated with an increased risk of skin necrosis. Treatment did not produce tissue fibrosis or necrosis or affect hair growth and color. The excellent tolerance of the skin and subcutaneous tissues allowed a second course of treatment to be done for recurrent tumors without increased local reactions. The high therapeutic index of the treatment, particularly for large tumors of the palpebrae, pinnae, and distal extremities, suggest that intratumoral chemotherapy with cisplatin is a good alternative to other available treatment modalities for equine sarcoïds.

References