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Objective—To determine outcome for equids with cutaneous neoplasms treated with cisplatin-containing biodegradable beads, alone or in conjunction with debulking.

Design—Retrospective case series.

Animals—56 horses, 1 zebra, 1 donkey, and 1 mule.

Procedures—Medical records were reviewed. Follow-up information was obtained through telephone conversations with owners and trainers of the animals.

Results—22 tumors were sarcoids, 6 were fibrosarcomas, 1 was a fibroma, 2 were peripheral nerve sheath tumors, 11 were squamous cell carcinomas, 14 were melanomas (13 gray horses and 1 bay horse), 1 was a lymphosarcoma, 1 was an adenocarcinoma, and 1 was a basal cell tumor. Forty-five (76%) animals underwent conventional or laser debulking of the tumor prior to bead implantation. Forty of 48 (83%) animals for which long-term follow-up information was available were relapse free 2 years after treatment. This included 20 of 22 animals with spindle cell tumors (including 11/13 horses with sarcoids), 6 of 10 animals with squamous cell carcinomas, 13 of 14 animals with melanomas, and 2 of 3 animals with other tumor types. Adverse effects were minimal.

Conclusions and Clinical Relevance—Results suggest that implantation of cisplatin-containing biodegradable beads, with or without tumor debulking, may be an effective treatment for equidae with various cutaneous neoplasms. (J Am Vet Med Assoc 2006;229:1617–1622)

Intrallesional administration of cisplatin has been commonly used for treatment of cutaneous tumors in horses and has been found to be effective against a variety of solid tumors.9,10 When used in this manner, the drug is mixed with sterile sesame oil and injected in a crosshatch pattern throughout the tumor site.6,7 Multiple injections are required with this technique (ie, 4 treatments administered at 2-week intervals). Difficulties have been found with the intrallesional injection technique, including difficulty in performing injections in periocular sarcoids,5 leakage of the cisplatin solution following injection,7 and unpredictability in the consistency and stability of the emulsion.5 There is also a risk of accidental injection for the veterinarian administering the cisplatin, especially if there is inadequate patient restraint or analgesia at the site of the injection.

For these reasons, various slow-release delivery systems that can be implanted at the tumor site, resulting in local diffusion of the chemotherapeutic agent, have been developed.11 In an unpublished pilot study, we found that implantation of cisplatin-containing biodegradable beads in healthy horses resulted in minimal local reactions and no systemic reactions. The purpose of the study reported here was to determine outcome for horses with cutaneous neoplasms treated with these cisplatin-containing biodegradable beads alone or in conjunction with debulking.

Criteria for Selection of Cases

Medical records of all horses admitted to the Marion duPont Scott Equine Medical Center between January 2000 and December 2004 for treatment of cutaneous neoplasms were reviewed. Horses were eligible for inclusion in the study if cisplatin-containing biodegradable beads had been used for treatment of the neoplasm.

Procedures

Information obtained from the medical records of horses included in the study consisted of history; physical examination findings, including size of the cutaneous mass; previous treatments, including previous cisplatin injections; perioperative and postoperative treatments; surgical procedure; number of cisplatin beads placed; results of histologic examination of portions of the mass; and results of follow-up examinations.

Cisplatin-containing biodegradable beads—The cisplatin-containing biodegradable beads were manufactured from a commercially available matrix material (calcium sulfate and dextran sulfate) to which cisplatin was added to a final concentration of 7%. Beads were molded in a 3-mm bead mold (Figure 1). Manufactured
beads weighed between 20 and 26 mg and contained approximately 1.6 mg of cisplatin/bead.1 Beads were sterilized by means of gamma irradiation and stored in the dark at room temperature until use.

Surgical procedure—Owners of all horses provided informed consent prior to the procedure. In particular, owners were informed that although intrallesional administration of cisplatin was an established procedure, implantation of cisplatin-containing biodegradable beads was investigational. Horses were treated with procaine penicillin G (22,000 U/kg [10,000 U/lb], IM, once) and phenylbutazone (2 g, IV, once) or flu-nixin meglumine (1.1 mg/kg [0.5 mg/lb], IV, once) prior to bead implantation.

Horses with small (ie, < 1.5 cm in diameter), accessible masses were treated by means of bead implantation alone. For this procedure, horses were sedated and mepivicaine hydrochloride was administered SC in the tissues surrounding the mass. A 1-cm stab incision was created adjacent to the mass with a scalpel blade, and a mosquito or Kelly forceps was used to grasp a cisplatin bead and insert it through the stab incision. An attempt was made to insert the bead at the deep margin of the mass. Following bead implantation, the incision was closed with 2-0 polyglactin 910 suture material. Additional cisplatin beads were grasped with a forceps and inserted through a stab incision that had been created with a scalpel blade. Each stab incision was then closed with a single cruciate suture of 2-0 polyglactin 910 suture material.

Following surgery, horses were treated with phenylbutazone (2.2 mg/kg, PO, q 12 to 24 h) and with trimethoprim-sulfamethoxazole (30 mg/kg [13.6 mg/lb], PO, q 12 h), doxycycline hyclate (10 mg/kg [4.5 mg/lb], PO, q 12 h), procaine penicillin G (22,000 U/kg, IM, q 12 h), or, for horses with periorcular lesions, a triple-antibiotic ophthalmic ointment. Two horses with open lesions were treated topically with 5 fluorouracil cream.

Bandages were applied postoperatively when possible or when tolerated by the horse. Owners were instructed to avoid skin contact with any discharge from the wounds and were asked to monitor for any swelling, discharge, erythema, alopecia, or regrowth of the mass.

Follow-up evaluation—Owners were directed to return their horses to the hospital after 30 days for reevaluation and implantation of additional cisplatin beads, if necessary. Additional cisplatin beads were implanted if there was regrowth of the tumor or, in horses that had undergone bead implantation only or debulking, the tumor was the same size or larger. Owners of horses in which additional beads were implanted were asked to return their horses for an additional follow-up evaluation 30 days later. Owners of horses in which additional beads were not implanted were instructed to monitor the site closely and to contact one of the authors (KES) if there were any changes.

For the present study, long-term (≥ 1 year) follow-up information was obtained through telephone conversations with the owners and trainers of affected horses. Treatment was considered to have failed if there was regrowth of the tumor after it had been removed,
no response to treatment, or growth of the tumor after treatment. In horses in which ≥ 2 tumors were treated, response to treatment was monitored for each tumor and treatment was considered to have failed if any 1 tumor did not respond to treatment.

Histologic evaluation—Biopsy specimens from all horses, except 2 horses with partial-thickness verrucous sarcomas in which biopsy was not performed to avoid creating full-thickness skin defects, were submitted for histologic examination. Spindle cell tumors that had the characteristic epidermal and dermal components were classified as sarcomas. Spindle cell tumors that lacked the epidermal component typical of an equine sarcoma but that had the characteristic fibroblastic component were classified as fibrosarcoma or fibroma. Other spindle cell tumors were classified as peripheral nerve sheath tumors, fibrosarcomas, and fibrosarcomas with myxomatous degeneration on the basis of typical appearance.

Results
Fifty-six horses, 1 zebra, 1 donkey, and 1 mule met the criteria for inclusion in the study. There were 40 geldings, 18 mares, and 1 stallion. The 56 horses included 15 Thoroughbreds, 8 Quarter Horses, 1 Saddlebred, 5 Arabians, 1 Welsh pony, 3 Irish Sport horses, 1 Cleveland Bay, 9 warmbloods (1 Belgian, 1 Dutch, 1 French, 1 Holsteiner, 1 Oldenburg, 2 unspecified warmbloods, 1 Thoroughbred-Hanoverian cross, and 1 Thoroughbred-Oldenburg cross), 1 Morgan, 4 Appaloosas, 1 Thoroughbred-Standardbred cross, 2 Standardbreds, 1 Belgian, 1 pony, and 3 crossbred horses. Mean age was 13.5 years (range, 3 to 29 years).

Number of treatments ranged from 1 to 19 (mean, 2.7; median, 2). There were 30 horses that received a single treatment; 10 that received 2 treatments; 8 that received 3 treatments; 3 that received 4 treatments; 2 that received 8 treatments; and 1 each that received 5, 6, 7, 9, 15, and 19 treatments. Treatment consisted of implantation of beads alone in 14 horses; conventional debulking (ie, with a scalpel) and bead placement in 27 horses; CO2 laser debulking and bead placement in 14 horses; gallium-aluminum-arsenide laser debulking and bead placement in 3 horses; and gallium-aluminum-arsenide laser debulking, CO2 laser debulking, and bead placement in 1 horse.

Histologic examination of biopsy specimens revealed that 22 tumors were sarcomas, 6 were fibrosarcomas (1 with myxomatous degeneration), 1 was a fibroma, 2 were peripheral nerve sheath tumors, 11 were squamous cell carcinomas, 14 were melanomas (13 in gray horses and 1 in a bay horse), 1 was a lymphosarcoma, 1 was an adenocarcinoma, and 1 was a basal cell tumor.

Spindle cell tumors—Thirty-one horses had sarcomas or other spindle cell tumors that were treated. Tumor locations in these horses included the ear (n = 1), neck (2), face (6), periorbital region (2), eyelids (4), ventral aspect of the abdomen (3), girth region (1), prepuce (1), inguinal region (3), axilla (1), gluteal region (1), thigh (3), fetlock region (1), tail (1), and coronary band (1).

Treatment in these horses consisted of implantation of beads alone (n = 10); conventional debulking and bead implantation (12); CO2 laser debulking and bead implantation (6); gallium-aluminum-arsenide laser debulking and bead placement (2); or gallium-aluminum-arsenide laser debulking, CO2 laser debulking, and bead placement (1; this horse had many large tumors that required multiple treatments over many months). Horses received a mean of 2.4 treatments (median, 2; range, 1 to 8). In 1 horse with a tumor involving the eyelid, fluorouracil was applied topically to an open lesion adjacent to the bead implantation site. The spindle cell tumors of 10 horses were treated with cisplatin beads alone. Twelve other horses were treated with surgical debulking in addition to bead implantation. Four had the tumors resected with the CO2 laser, and 3 had the tumor vaporized with the CO2 laser (1 horse) or gallium-aluminum-arsenide laser (2 horses). One horse with many large tumors was treated over many months with surgical debulking, hyperthermia, the CO2 laser, and the gallium-aluminum-arsenide laser before final resolution. One horse had 5 fluorouracil applied to an open lesion adjacent to the bead implantation site on an eyelid, which resolved the tumor.

Nine of the 31 horses with spindle cell tumors were lost to follow-up. Of the remaining 22 horses for which follow-up information was available, 20 (91%) had resolution of the tumor for at least 2 years after treatment, including 11 of 13 horses with sarcomas. One zebra was euthanized because of regrowth of an ulcerated fibroblastic sarcoma around the left eye despite 3 treatments with cisplatin beads over a period of 6 months. Recommendations for monthly reexamination were not followed in this case, in part because the animal had to be anesthetized for examination and treatment. One horse with a large verrucous sarcoma treated by means of bead implantation alone had an increase in size of the tumor over the 6 months after treatment.

Three horses for which follow-up information was available had growth of a tumor adjacent to the original tumor site ≥ 2 years after the original treatment. All of these tumors were diagnosed as sarcomas, and all 3 horses were tumor free ≥ 2 years after repeat treatment. One horse with a peripheral nerve sheath tumor involving the upper eyelid eventually required enucleation, presumably because of adverse effects of cisplatin on the cornea.

Squamous cell carcinoma—Eleven horses had squamous cell carcinomas that were treated. Tumor locations included the prepuce (n = 4), vulva (2), perianal region (1), eyelid (3), and nares and upper lip (1). Treatment consisted of implantation of beads alone (n = 1), conventional debulking and bead implantation (5), CO2 laser debulking and bead implantation (4), and gallium-aluminum-arsenide laser debulking and bead placement (1). Horses received a mean of 2 treatments (median, 1; range, 1 to 19). In 1 horse with a tumor involving the eyelid, fluorouracil was applied topically to an open lesion adjacent to the bead implantation site.
Discussion

Results of the present study suggest that implantation of cisplatin-containing biodegradable beads, with or without tumor debulking, is an effective treatment for equidae with various cutaneous neoplasms. Bead implantation can be considered a simpler alternative to cisplatin injections, if desired by the veterinarian. In this study, 40 of 48 (83%) horses for which long-term follow-up information was available were relapse free 2 years after treatment. This included 20 of 22 horses with spindle cell tumors (including 11/13 horses with sarcoids), 6 of 10 horses with squamous cell carcinomas, 12 of 13 horses with melanomas, and 2 of 3 horses with other tumor types.

The cisplatin-containing biodegradable beads used in the present study consisted of an inorganic biopolymer composite of calcium sulfate and dextran sulfate mixed with an aqueous biopolymer solution containing the cisplatin. The resulting slurry solidifies, entrapping the cisplatin. Unpublished data indicate that the cisplatin concentration in the beads is 7%; that the beads are stable for at least 1 year when maintained in a dark, cool environment; and that implantation of beads in healthy horses typically results in no more than mild, local swelling that lasts up to 24 hours.

Cisplatin has previously been demonstrated to be effective in treating various neoplasms in horses. One study, for instance, reported 1-year relapse-free rates of 87% (18/19) for horses with sarcoids and 65% (5/7) for horses with squamous cell carcinoma treated with intralesional injection of cisplatin in sesame oil. A subsequent study reported a relapse-free rate of 92% (26/28) following intralesional injection of cisplatin in sesame oil for treatment of horses with cutaneous tumors. Results of the present study were similar to results of these previous studies.

In the authors' opinion, implantation of cisplatin beads is more convenient and more precise than intralesional injection of a cisplatin-sesame oil emulsion. The pattern of bead insertion can be modified as necessary, depending on the size and texture of the tumor being treated. Additionally, large areas for which injection of a cisplatin-sesame oil emulsion would be impractical can be efficiently treated with cisplatin beads. We currently recommend monthly reevaluation with possible implantation of additional beads, depending on the response to treatment. Most horses in the present study received only 2 treatments, in contrast with the 4 treatments recommended with use of the cisplatin-sesame oil emulsion.

Four horses with sarcoids in the present study that underwent cisplatin bead implantation had previously received intralesional cisplatin injections. Because the injections were not performed at the authors' hospital, the protocol for these injections was not known. However, all 4 of these horses had resolution of the tumors for ≥2 years after cisplatin bead implantation.

Two horses with eyelid tumors in the present study were treated with 5 fluorouracil topically following cisplatin bead implantation. Thus, it could not be determined whether resolution of the tumors in these horses was a result of cisplatin bead implantation, fluorouracil treatment, or a combination of the 2.
Twenty-seven of 59 (46%) horses in the present study underwent conventional debulking of the tumor prior to cisplatin bead implantation, and an additional 18 underwent laser debulking. Debubling is important because antineoplastic agents are most effective when the tumor burden is low. Furthermore, tumor cells that remain after resection of a mass are likely to have an accelerated rate of growth, and cisplatin has been reported to be most effective during the period when tumor burden is low and tumor cell activity is high. For horses in the present study, cisplatin beads were always placed along the margin of lesions where unapparent tumor cells could reside. In horses with large wounds, beads were also implanted within the interior of the lesion.

A CO$_2$ or gallium-aluminum-arsenide diode laser was used in 18 horses in the present study. Energy from the CO$_2$ laser is highly absorbed by water in the tissues, resulting in vaporization of cells on the surface of the tumor bed that are contacted directly by the laser. However, tissue penetration is superficial with a CO$_2$ laser, and this laser should not be relied on to kill tumor cells beyond the visible surface. Success rates of 62% and 72%$^{15}$ have been reported following CO$_2$ laser resection of sarcoids in horses, compared with a success rate of 85% (11/13) for horses with sarcoids in the present study.

The gallium-aluminum-arsenide diode laser was used to vaporize masses in 3 horses in the present study. Laser light of the wavelength that was used is absorbed poorly by lightly pigmented tissue but is absorbed to a great degree by darkly pigmented tissues. Although tissue penetration can be substantially greater with this laser than with a CO$_2$ laser, the photothermal effects of this laser on specific tumor cells is unknown, and this laser should not be depended on to affect tumor cells beyond the area of visible tissue effect.

Owners of 10 horses in the present study reported postoperative swelling and inflammation similar to that seen following intrallesional injection of cisplatin. One horse that had an axillary sarcoid removed had drainage at the excision site; the tumor resolved even though the beads were possibly lost prematurely. The horse had received the prescribed postoperative stall confinement. One horse eventually required enucleation, presumably because of adverse effects on the cornea caused by cisplatin beads implanted in the upper eyelid. The minimal amount of soft tissue in the eyelid region may result in high local concentrations of cisplatin, and complications have been previously reported following cisplatin treatment of periorbital lesions.$^7$

Monitoring the results of cisplatin treatment was fairly straightforward for horses in the present study that underwent bead implantation alone and for horses with open wounds allowed to heal by second intention. These lesions often required longer than 1 month to resolve, but continual improvement was generally seen. In contrast, monitoring the results of treatment in horses that underwent tumor excision with primary closure of the wound was more difficult. Because of difficulties in observing tumor recurrence and a tendency for persistence after apparent remission, the authors currently recommend that chemotherapy be continued well beyond the time of apparent healing. However, the duration of treatment in these horses remains subjective. Most horses in the present study underwent 2 to 3 episodes of cisplatin bead implantation, and this 2- to 3-month duration of treatment is similar to that reported for intralesional cisplatin injection.$^7$ However, some tumors in the present study required additional treatments to achieve resolution. It is unknown whether additional treatment could have resulted in resolution of the tumor in the horse with a sinus adenocarcinoma, but a 2-year remission time is not characteristic for this type of tumor in horses.

Injection of a chemotherapeutic agent into a tumor mass can cause systemic effects because of rapid absorption of the drug from the injection depot.$^{16}$ For this reason, a variety of matrices that slow the release of chemotherapeutic agents have been studied. In 1 study,$^7$ use of a collagen-based matrix was less effective in mice with fibrosarcoma than was IV administration of cisplatin, although there was a longer delay in growth of the tumor following use of the matrix and lower risk of systemic toxicoses. Use of an open-cell polylactic acid polymer with 8% cisplatin delayed local growth and metastasis following marginal resection of mammary carcinoma in mice,$^7$ and implantation of the same type of polymer with 2.2% cisplatin adjacent to the allograft in dogs undergoing limb-sparing surgery because of osteosarcoma resulted in sustained high local concentration of the drug without signs of systemic toxicosis.$^{11}$

The required tissue concentration of cisplatin for treatment of tumors in horses has not been established, but a concentration of 1 mg/cm$^3$ has been shown to be effective for some equine tumors.$^{24}$ Results of unpublished pilot studies suggest that implantation of the cisplatin-containing biodegradable beads used in the present study with a 2-cm spacing between beads results in comparable local cisplatin concentrations.

Because control groups were not included in the present study, it was not possible to definitively determine whether results obtained with bead implantation were better than results that could have been obtained with surgery alone or even better than results of no treatment. However, because these types of tumors have a well-known tendency to recur, our findings suggest that cisplatin bead implantation resulted in higher success rates than could be expected with surgery alone.

In conclusion, results of the present study suggest that implantation of cisplatin-containing biodegradable beads is a safe and effective method for treating cutaneous neoplasms in horses. Success rate in the present study was similar to rates reported following intrallesional injection of cisplatin.$^7$ For small tumors (< 1.5 cm in diameter), bead implantation alone was generally effective, whereas for larger tumors (≥ 1.5 cm in diameter), debulking followed by bead implantation was used. At the time of the present study, the cost of the beads was $5/bead.$^7$ Overall treatment cost, therefore, will depend on the number of beads used. The ease of implantation, the potential need for fewer treatments, and the greater safety for the operator make the beads a favorable alternative to the intrallesional injection of cisplatin for treatment of tumors in horses.
b. Cisplatin, Sigma Chemical Co, St Louis, Mo.
c. Investigational New Animal Drug 10-829, Royer Biomedical Inc, Frederick, Md.

References