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Field Safety Experience With an Autologous Cancer Vaccine in 41 Horses: A Retrospective Study (2019–2021)

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ABSTRACT

Autologous cancer vaccines (ACV) are an emerging option for adjuvant cancer treatment in veterinary medicine. With this form of active immunotherapy, the patient's tumor cells are processed *ex vivo* and returned to the patient with the goal of stimulating an immune response to unique, patient-specific antigens. The case accession database at Torigen was queried to identify horses that underwent biopsy or surgical resection of their primary tumor and received at least one subcutaneous dose of an adjuvanted whole-cell autologous cancer vaccine. The records were then reviewed for any reported adverse events (AE). Forty-one horses met the inclusion criteria and received 252 doses of Torigen's ACV (ACV-T). There were seven AEs reported in four horses, which were associated with 1.6% of the administered doses of the ACV-T. Of the reported AE, all were characterized as mild. The ACV-T appears to be well tolerated by horses, and may be useful as a treatment option for owners who are concerned about AEs that can occur with other types of adjuvant cancer therapy. Additional studies are warranted to evaluate the efficacy of this ACV in horses with solid tumors.

1. Introduction

Cutaneous neoplasms reportedly occur as 30%–65% of all skin lesions in horses. Of those cutaneous neoplasms, melanoma, sarcoids, and squamous cell carcinoma account for 75% [1,2]. Depending on location and biologic activity, tumors of the skin and external genitalia can become debilitating in late-stage disease. Tumors that develop in the areas of the girth, bridle path, and other sensitive locations may result in loss of use of the affected horse. Surgical removal is often the first intervention, although post-operative recurrence rates are reported as high as 82% [3–10]. These tumors recur because they can often manifest in challenging locations making *en bloc* resection difficult given the limited reconstruction techniques available. Horse owners may also delay seeking medical care, resulting in larger lesions that are more difficult to address surgically. Given the high likelihood of local recurrence, adjuvant therapies are often used following surgical resection. Chemotherapy (intralesional, topical, and/or systemic), electrochemotherapy, cryotherapy, and radiation therapy have been used postoperatively to reduce the risk of tumor recurrence with variable success [5,7,11–16]. Despite the focal nature of postoperative therapy, problematic adverse events (AEs) have been reported in up to 60% of horses including tissue necrosis, non–healing wounds, and scar contracture [10,17–20]. Radiation therapy and electrochemotherapy have additional concerns relating to the risks of morbidity and mortality associated with multiple episodes of general anesthesia [21]. Radiation therapy and electrochemotherapy also may not be readily available, and regulatory compliance challenges in handling and administering hazardous drugs may decrease the willingness of some veterinarians to continue providing intralesional chemotherapy. Also, local adjuvant treatments are unlikely to affect the risk for metastasis. These limitations demonstrate the need for safe and accessible treatment options for horses with solid tumors.

☆ Conflict of interest statement: CBG, RMC, MAS, AEK, and MDL have a financial interest in Torigen Pharmaceuticals, Inc as employees or shareholders. MAS is co-inventor of this technology.

Ethical statement: Before the vaccine was produced and administered, written owner informed consent was obtained as required by the United States Department of Agriculture Center for Veterinary Biologics for experimental autologous prescription products.

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Immunotherapy is becoming commonplace during human cancer treatment and has taken the forms of immune checkpoint inhibition, increasing the cytotoxic T-cell response, and destabilization of the tumor microenvironment [22,23]. Autologous cancer vaccines (ACV) are a type of individualized immunotherapy using the patient's own cancer tissue as the source of both tumor- and patient-specific antigens [24]. Although specific methodology may vary, the general process involves *ex vivo* manipulation of the tumor to create the ACVs that are administered to the patient with the goal of stimulating humoral and cell-mediated immune responses against multiple personalized antigens [22]. Before administration to the patient, cancer cells in the ACVs are inactivated by irradiation, fixation, or lysis [12,25–27].

ACVs have been described previously for use in horses but have been limited to use in sarcoids and melanoma [12,28–30]. One technique described included surgically implanting flash-frozen sarcoid tissue cubes just ventral to the nuchal ligament. Swelling of the implantation site, fever, and abscessation were reported in 43.8% of treated horses [28,29]. Another ACV technique described for sarcoids was an intradermal vaccination with polymerized protein given every 4 weeks until surgical site healing was noted. AEs included swelling and erythema of the injection site; however, the actual number of horses was not reported [30,31]. A whole-cell ACV (cells cryopreserved and irradiated) for melanoma was administered subcutaneously every other week for 6 weeks then every 6 weeks. The adjuvant for this ACV was only included for the first vaccines due to reported local reactions. The number of horses affected and the severity of AEs for this ACV were not reported [12].

The ACV used in the present study (ACV-T) applies a novel method to ACV manufacturing. The ACV-T utilizes mechanical cell dissociation to include mutated antigens from both the tumor cell as well as the tumor microenvironment. This whole cell tissue vaccine has a low rate of mild AEs reported in dogs and cats. Twelve percent of dogs and 5% of cats were reported to have an AE after vaccination with the ACV-T [26,32,33]. The purpose of this study was to evaluate the frequency and severity of AEs reported in horses treated with this adjuvanted whole tissue ACV-T that is straightforward to administer under typical field conditions for multiple tumor types.

2. Materials and methods

2.1. Autologous cancer vaccine protocol

Preparation of the ACV-T has been described elsewhere [26]. Briefly, after surgical excision, unfixed tumor tissue was shipped overnight on cold packs to the commercial laboratory (Torigen Pharmaceuticals, Farmington, CT) for preparation of the ACV-T. Tumor tissue was mechanically dissociated into a cell suspension, inactivated with 2.5% glutaraldehyde, and combined with an extracellular porcine protein matrix immunomodulator adjuvant (MIMSIS; Cook Biotech, West Lafayette, IN). The ACV-T was placed into a sterile vial and shipped overnight on cold packs to the submitting veterinarian.

Before the vaccine was produced and administered, written owner informed consent was obtained as required by the United States Department of Agriculture Center for Veterinary Biologics for experimental autologous prescription products. Veterinarians were instructed to give a 1 mL dose of the ACV-T via subcutaneous injection once every 7 days for six total doses. The attending veterinarian was further instructed to monitor the horse for acute AEs for 30 minutes after each injection. At the time of each injection, horse owners were also informed of possible vaccine reactions and instructed to report any observed abnormalities immediately upon their occurrence.

2.2. Case selection

The case accession database at Torigen Pharmaceuticals was queried to identify all equine patients from August 2019 to May 2021. Horses were eligible for inclusion in this study if they had a histopathologic, cytologic, or morphologic diagnosis of cancer or sarcoid and received at least one dose of the ACV-T. Horses were excluded from study if they did not receive at least one dose of the ACV-T or had incomplete case information. Histopathologic and cytologic diagnoses were reported by board-certified veterinary pathologists via commercial laboratory services. Morphologic diagnoses were reported by the attending veterinarian based on signalment and location and gross appearance of the lesions. Patient data collected included signalment, body weight, histopathology or cytology results, and any AE reported after the administration of the vaccine. Information on each horse was obtained through direct communication with the attending veterinarian. An AE was considered any observation that was unfavorable and unintended and occurred after use of the ACV-T, whether the observation was considered to be related to the ACV-T administration [34]. All reported AE were classified with respect to severity and relatedness based on the Veterinary Comparative Oncology Group – Common Terminology Criteria for Adverse Events (VCOG-CTCAE v2) [35].

2.3. Statistics

Descriptive statistics were generated using commercial software (Prism 9, GraphPad Software, LLC, 2021, San Diego, CA). Results are reported as mean ± standard deviation unless otherwise noted.

3. Results

3.1. Study population

There were 76 horses identified in the database. Of those, 41 horses met the entry criteria, and 35 horses were excluded based on histopathological findings, or the attending veterinarian or horse owner opting to pursue other treatment options. The American Quarter Horse (19.5%) was the predominant breed in this population. The mean age was 14.7 ± 5.86 years, and the mean weight was 503.6 ± 80.12 kilograms within the study population. Stallions and geldings were reported more frequently (58.5%) than mares. Histopathology was done in 31 (75.6%) of horses, and morphologic diagnoses were reported by the attending veterinarian for 10 horses (7 melanoma, 3 sarcoid). No tumors were diagnosed by cytology. The most common tumor was melanoma (63.4%) followed by sarcoid (24.4%), squamous cell carcinoma (9.8%), and lymphoma (2.4%).

During the study period, there were 252 doses of the ACV-T administered to 41 horses. The mean number of vaccine doses administered per horse was 6.2 ± 0.94 (median 6; range 6–12). One horse with melanoma developed new cutaneous masses 14 months after initial surgery and the ACV-T administration and was treated with 6 additional doses of the ACV-T. Summary data are presented in Table 1.

This population of horses was geographically dispersed across the United States with tumor specimens submitted from 13 different states. The largest proportion of cases came from New York (24%) and Georgia (15%). Thirty (73%) cases were submitted by general practitioners and 11 (27%) were submitted by specialists (surgeons and internists). Eight (20%) horses were treated with additional cancer therapy concurrently with the ACV-T including a canine melanoma DNA vaccine (Oncept, Boehringer Ingelheim, Duluth, GA), intralesional chemotherapy, post-operative cisplatin bead implantation, and cryotherapy.

Table 1
Summary data from 41 horses treated with an autologous cancer vaccine.

Variable	
Age, y (n = 41; mean ± SD)	14.7 ± 5.86
Range	2 – 27
Weight, kg (n = 37; mean ± SD)	503.6 ± 80.12
Range	273 – 818
Sex	
Stallion	2 (4.8%)
Gelding	22 (53.7%)
Mare	17 (41.5%)
Breeds	
American Paint Horse	4 (9.8%)
American Quarter Horse	9 (21.9%)
Andalusian	3 (7.3%)
Arabian	2 (4.8%)
Clydesdale	1 (2.4%)
Crossbred and/or Grade	7 (17.1%)
Irish Sport Horse	1 (2.4%)
Morgan	1 (2.4%)
Oldenburg	3 (7.3%)
Thoroughbred	5 (12.2%)
Trakehner	1 (3.6%)
Warmblood	3 (7.3%)
Welsh Pony	1 (2.4%)
Cancer type	
Melanoma	26 (63.4%)
Sarcoid	10 (24.4%)
Squamous cell carcinoma	4 (9.8%)
Lymphoma	1 (2.4%)
Doses of Torigen Autologous Cancer Vaccine administered	252
Doses per horse (mean ± SD)	6.2 ± 0.94
Median	6
Range	6 – 12
Adverse events	7
Horses affected	4 (9.8%)
Doses associated with AE	4 (1.6%)
Doses associated with serious AE	0 (0.0%)

3.2. Adverse events

During the study period, there were seven AEs reported in 4 (9.8%) horses, which were associated with 4 of 252 (1.6%) doses of the ACV-T. Of the four AEs reported, two were in horses without histopathologic diagnosis (one presumptive melanoma and one presumptive sarcoid) and two were in horses with histopathologic confirmation of melanoma. The AEs were classified as mild (grade 1). Individual case data are presented in Table 2. The most commonly reported AE was injection site swelling, occurring in two horses. One horse with a recurrent, metastatic melanoma had 4 (57%) of the reported AEs including a diminished appetite, lethargy, a non–healing surgical wound at the surgery site, and ventral edema. Information provided by the attending veterinarian did not allow for assigning a grade to the AEs reported in this horse.

4. Discussion

This study is the first report of a whole tissue adjuvanted ACV administered to horses with multiple tumor types. The horses described herein were diagnosed with melanoma, lymphoma, squamous cell carcinoma (SCC), and sarcoid in contrast to previous reports of ACV that were used to treat only sarcoids and melanoma. The mean age of horses with sarcoid was 8.2 years, SCC 14.5 years, lymphoma 11 years, and 15.8 years for melanoma, which are similar to previous reports [1,2,4,6,28]. Males were overrepresented in the current population (58.5%), which is similar to previous studies with 66%–83% male horses [28,30]. The American Quarter Horse was the most common breed reported in this study population. Comparing breed distributions among various studies is challenging given limited breed data reported in some studies, which is further complicated by studies done worldwide with differing breed frequencies. Histopathology was available in 31 (75.6%) of horses, and morphologic diagnoses were reported by the attending veterinarian for 10 horses (7 melanoma, 3 sarcoid). Although histopathology is critical to establish an accurate diagnosis and prognosis, morphologic diagnoses were included in this group of horses to reflect typical field conditions. Unlike previous reports of ACV in cancer-bearing horses, the present study involved multiple treatment centers, and cases were managed by an admixture of general practitioners and specialists, which also reflects real-world use of the ACV-T.

Of the seven AE reported in four horses, four occurred in a single Andalusian stallion with metastatic melanoma (Table 2). Before the surgical procedure for the ACV-T production, this horse had undergone surgical excision of perianal melanomas, followed by coarse-fractionated external beam radiation therapy and intralesional chemotherapy, which may have contributed to the non–healing wound reported by the attending veterinarian. This horse was also treated with a canine melanoma vaccine (Oncept; Boehringer Ingelheim, Duluth, GA). Because this horse had a significant disease burden, the diminished appetite and edema were most likely a result of progressive and metastatic disease rather than due to the ACV-T administration. Two horses were reported to have injection site swelling, however, one of the ACV-T injections was inadvertently given intradermally instead of subcutaneously. The other horse was reported to develop urticaria following the 5th dose of the ACV-T and resolved with a single dose of oral steroid. This horse had a previous history of seasonal urticaria, and urticaria was not observed after the 6th dose of the ACV-T. The AE rate in this group of horses (9.8%) was lower than previously reported in 93 dogs (11.8%) and higher than reported in cats (5.1%) treated with the same ACV [26,33]. It is unclear if the observed difference in AE rates between cats and horses reflects a difference between species or is due to the smaller equine study population. These observations suggest that horses treated with the ACV-T tolerate this form of immunotherapy with a low risk for mild AE. It is noteworthy that horses described herein were treated with a series of six doses compared to the three doses used in the canine and feline studies. Six doses of the ACV-T were used for this population of horses due to lack of tumor response noted in one author's (MAS, personal communication) earlier evaluation of three doses of the ACV-T in horses, and the observation that cats treated with >3 doses of the ACV-T had no higher rate of AEs [33]. The 9.8% observed rate of AEs with the ACV-T was lower than the 43.8% rate reported with the autologous cancer vaccine method of surgically implanting flash-frozen sarcoid tissue cubes [28]. Given the method of reporting AEs (swelling at the implantation site, fever, and abscessation) in the frozen tissue implantation study, it is impossible to directly compare their severity with those described with ACV-T [28,29]. Also, the adverse effects observed in the ACV-T treated horses were mild (mild injection site swelling) which is similar to polymerized ACV (mild injection site swelling and erythema) [30].

One strength of the present study is the comparatively large number of horses (41) treated with the ACV-T relative to previous reports of other ACVs. Twenty-one horses were evaluated with a polymerized protein ACV [30], 33 total horses have been evaluated

Table 2
Adverse events reported in four horses treated with an autologous cancer vaccine.

Patient ID	Breed	Age (y)	Sex	Weight (kg)	Cancer	Associated Dose	Reported Adverse Event	Grade[a]	Relatedness[b]
20–065	American Quarter Horse	17	MC	591	Melanoma	5	Dermatologic and/or skin: Urticaria (hives, welts, wheals)	1	2
20–203	Andalusian	15	MC	545	Melanoma	6	Administration site conditions: Other (injection site swelling)	1	5
20–376	Andalusian	19	MI	530	Melanoma	NR[c]	Dermatologic and/or skin: Other (delayed wound healing)	-	2
						NR	Gastrointestinal: Appetite, altered	-	2
						NR	Dermatologic and/or skin: Edema, localized	-	2
						NR	Constitutional clinical signs: Lethargy and/or fatigue	-	2
20–380	Mix	6	F	500	Sarcoid	2	Administration site conditions: Other (injection site swelling)	1	4

MC, male, castrated; MI, male, intact; F, female, intact
[a] 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = death related to AE, - = insufficient data to grade
[b] 1 = unrelated, 2 = unlikely, 3 = possible, 4 = probable, 5 = definite
[c] NR = not reported

with a surgically implanted frozen tissue ACV for sarcoids [28,29], and 12 horses treated with an irradiated and adjuvanted ACV [12]. Evaluating horses treated in typical clinical settings in varying locations may also provide a more accurate representation of expectations following treatment with this ACV. Another strength of this study is the method of AE reporting. The VCOG-CTCAE v2 [35] was used in the present study and represents the first application of this tool for AE reporting in equine immunotherapy. This categorization scheme was initially developed for use in dogs in cats, and in the absence of a similar instrument for horses, provides a meaningful way to systematically categorize and communicate the severity and relatedness of AE to cancer treatment.

A limitation of this study is the retrospective nature of case reviews. There is potential for failure of either the horse owner or attending veterinarian to report observed AEs. This could potentially bias the conclusions by underestimating the AE rates in this population of horses. Incomplete information may also be encountered when searching a medical database and reviewing medical records. In human clinical trials, where patients can directly report AEs, they often provide limited information for the attending physician preventing AE grading [36]. Comparing patient-reported AEs to physician-reported AEs, the patient-clinician agreement was found to be poor to moderate, and this discrepancy was due to physician underreporting [37]. In veterinary cancer trials, AE reporting may be similarly suboptimal [38].

The low rate of reported AE with the ACV-T may be appealing to some horse owners. A survey of dog and cat owners revealed that the majority would not pursue chemotherapy for their pets with cancer [39]. Depending on the use of the horse, some horse owners may be reluctant to pursue traditional cancer treatments (surgery, radiation therapy, or chemotherapy) due to the risks for morbidity and mortality [18,20,21]. Indeed, AEs may affect 27%–60% of horses undergoing cancer treatment [18–20]. Many of the reported AEs are not trivial, and include acute respiratory difficulty, bone marrow suppression, corneal ulceration, colic, non–healing wounds, scar contracture, and thrombophlebitis [18,20].

Although immunotherapy is commonplace in human oncology, and increasing options are becoming available for companion animals, it is conceivable that this approach will also be useful in equine oncology. The individualized active immunotherapy with the ACV-T may become a viable option for horses with solid tumors. These findings suggest the ACV-T is well-tolerated by horses in the post-operative setting under typical field use conditions. Given the apparent low risk to treated horses, further studies to establish the efficacy of the ACV-T in equine cancer patients are warranted.

5. Conclusions

As an active form of immunotherapy, the ACV-T may be useful for decreasing the risk of tumor recurrence following surgery in horses. AEs were infrequently reported in this population of horses treated with the ACV-T, under typical field conditions. The reported AEs were low grade and consistent with AEs previously described in dogs and cats treated with the ACV-T [26,33]. Therefore, the ACV-T may be a potential adjuvant treatment for horse owners concerned about AEs associated with other cancer treatments, such as local chemotherapy or radiation therapy. These findings justify prospective studies to determine the efficacy of the ACV-T in horses with solid tumors.

CRediT author statement

Chelsea Greenberg: Data Curation, Writing – Original Draft; Laura H. Javsicas: Investigation, Writing – Review and editing; Ryan M. Clauson: Investigation, Writing – Review and editing; Mark A. Suckow: Conceptualization, Writing – Review and editing; Ashley E. Kalinauskas: Funding acquisition, Writing – Review and editing; Michael D. Lucroy: Formal analysis, Supervision, Visualization, Writing – Review and editing.

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