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Evaluation of Hematologic Parameters in 40 Dogs Receiving Long-Term Cytarabine for Meningoencephalomyelitis of Unknown Etiology

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Abstract

Background: Cytarabine (CA) is a commonly used adjunctive therapy for meningoencephalomyelitis of unknown etiology (MUE). Reported hematologic side effects include leukopenia, thrombocytopenia, and anemia. These have historically been reported more frequently in veterinary or human oncology patients receiving CA at chemotherapeutic doses rather than in dogs treated for MUE. Frequent CBC monitoring is considered standard practice following treatment with CA, but the added cost and time of monitoring may be deterring factors for owners when choosing adjunctive MUE therapies. Hypothesis/Objectives – Our aim was to evaluate hematologic parameters in dogs treated long-term (>6 months) with CA within a therapeutic range of 200-400mg/m2 at a minimum of every 3-4 weeks for clinically diagnosed MUE with the goals of developing appropriate monitoring recommendations and reporting adverse effects (AE). We hypothesized that there would be minimal to no evidence of myelosuppression or other AE.

Animals: 40 client-owned dogs with a clinical diagnosis of MUE.

Methods: Multicenter retrospective study. Hemograms pre- and post-treatment with CA were evaluated for changes in blood cell counts. Non-hematologic AE were categorized by severity and potential cause.

Results: No statistically significant cytopenias were seen. Non-hematologic AE potentially attributable to corticosteroids and CA therapy were reported in ten patients. One patient had mild AE directly attributable to CA.

Conclusions and Clinical Importance: The use of corticosteroids and CA at the described dosages has infrequent effects on hematologic parameters and is safe for long-term use in dogs with MUE. Our results support a reduction in the frequency of CBC monitoring during MUE treatment with CA.

Keywords: Cytarabine; Immunosuppressive Drugs; Granulomatous Meningoencephalitis; Adverse Effects; Myelosuppression; Hematologic Monitoring

Abbreviations: CNS: Central Nervous System; AE: Adverse Effects; CA: Cytosine Arabinoside; MRI: Magnetic Resonance Imaging; CSF: Cerebrospinal Fluid; CRI: Continuous Rate Infusion; RBC: Red Blood Cell Count; WBC: White Blood Cell Count; VCOG: Veterinary Cooperative Oncology Group.

Introduction

Meningoencephalomyelitis of unknown etiology (MUE) is a common cause of inflammatory disease in the central nervous system (CNS) of dogs [1-3]. This umbrella term encompasses several histologically distinct diseases, including granulomatous meningoencephalitis, necrotizing meningoencephalitis, and necrotizing leukoencephalitis [1-3]. While immunosuppressive doses of corticosteroids are generally accepted as a mainstay of therapy, complications of long-term steroid usage, as well as the guarded prognoses these diseases still carry, have led to the use of adjunctive immunomodulatory drugs in the treatment of MUE. Multi-drug therapy has been reported to improve outcomes in dogs treated with a variety of secondary agents compared to steroids alone [4-10]. Due to the immunomodulatory nature of these drugs, careful monitoring of adverse effects (AE) is crucial.

Cytarabine (cytosine arabinoside (CA)) is one such second-line drug that has become a part of many MUE treatment protocols [3-6,8,11-14]. Cytarabine is an S-phase-specific, synthetic pyrimidine analogue that competitively inhibits DNA polymerase in mitotically active cells, thereby inhibiting DNA synthesis and repair; additionally, it also causes topoisomerase dysfunction and inhibits ribonucleotide reductase and glycoprotein synthesis [2-3,5,15-19]. In addition to its use as an adjunctive MUE therapy, CA has also been used in combination protocols for canine and feline lymphoma and leukemias at doses up to 600 mg/m^2 [20-24].

Reported adverse hematologic effects of CA include leukopenia (primarily neutropenia), thrombocytopenia, and more rarely, anemia [16-17, 19-23, 25-28]. Non-hematologic AE of CA may include gastrointestinal side effects (anorexia, nausea, vomiting, diarrhea), lethargy, mild hair coat and skin changes, calcinosis cutis, conjunctivitis, oral ulceration, neurotoxicity, hepatotoxicity, and fever [5,14,20,29], though reports of such AE are uncommon in veterinary patients. The hematologic side effects have historically been reported more frequently in cohort studies and case series involving veterinary patients with cancer receiving the drug at chemotherapeutic doses with or without other chemotherapy drugs [20-24,26] or in human patients [16-17,19,25,27,30], rather than in dogs being treated for MUE (200-400 mg/m2). Several cohort studies evaluating the efficacy and safety of combined CA and prednisone/prednisolone for MUE did not identify evidence of myelosuppression [5-6,8,11-12]. However, the CA doses in these studies varied and were often lower (100-200 mg/m2) than many clinicians use for MUE, monitoring times varied or were not reported, or sample sizes were small.

Despite the conclusions drawn in these studies, regular monitoring of blood cell counts in patients treated with CA is common practice with recommendations including every 3 weeks during treatment, 1 week after each dose, or weekly for one month and then immediately before each subsequent dose [3,5,11,13-14,31]. The added cost and time required for this monitoring may be deterring factors for owners when choosing a second-line drug in the treatment of MUE. A larger, long-term study of the hematologic side effects in dogs treated with CA for MUE would help to characterize the actual incidence of such adverse events and better direct monitoring recommendations.

This multicenter retrospective study aimed to evaluate hematologic parameters in dogs treated long-term (>6 months) with CA for clinically diagnosed MUE with the goals of developing appropriate monitoring recommendations and reporting AE. We hypothesized that there would be minimal to no evidence of myelosuppression on CBC analysis or non-hematologic AE secondary to long-term treatment with CA at typical doses used for MUE (200-400 mg/m2).

Materials and Methods

Animals

All animals were client-owned dogs that were presented to one of three institutions (Carolina Veterinary Specialists-Matthews, Carolina Veterinary Specialists-Winston-Salem, NC State University, Veterinary Hospital). Medical records were searched for patients treated with CA from 2013-2018. Inclusion criteria consisted of a clinical diagnosis of MUE (see below), treatment with corticosteroids and CA for a minimum of 6 months, a CBC performed prior to starting CA, and serial CBCs performed throughout the study period following CA administration. Included cases had to have documentation of signalment; neurologic signs; concurrent diseases; the results of CBCs, serum chemistry panels, cerebrospinal fluid (CSF) analysis, and magnetic resonance imaging (MRI) findings; and CA dose, route, and treatment dates. Dogs were excluded if they received treatment with immunomodulatory drugs other than corticosteroids and CA at any point within the same treatment interval as CA.

Diagnosis

A presumptive clinical diagnosis of MUE was made based on guidelines suggested by a recent meta-analysis [4].

Specifically, dogs were considered to have MUE if they were older than 6 months; had evidence of single, multiple, or diffuse intracranial or spinal cord intraparenchymal lesions on MRI; had a CSF pleocytosis (total nucleated cell count [TNCC] >5 nucleated cells/ul) with >50% mononuclear cells; and had negative infectious disease serologic testing or strong clinical suspicion of absence of infectious diseases given clinical history (specifically, a lack of progression of signs with immunosuppression). One deviation from these guidelines was the inclusion of those patients with meningomyelitis of unknown etiology (i.e. no intracranial lesions), provided they fulfilled the other criteria for presumptive diagnosis [4].

Treatment

Cytarabine dosages ranged from 200-400 mg/m^2 per treatment session. The route of administration was either SC or IV continuous rate infusion (CRI). A treatment session was defined as drug administration over a time period from 8 hours to no more than 48 hours. Corticosteroid dosages also varied based on the individual patient's response to therapy.

Hematologic Monitoring

Complete blood counts with automated differential counts were performed at non-standardized time intervals based on clinician recommendations and, ultimately, on client compliance. Hematologic values evaluated included red blood cell count (RBC), white blood cell count (WBC), WBC differential count, and platelet count.

Statistical Analysis

The CBCs were analyzed in SAS (Version 9.4, Cary, NC). The data were grouped into 'rounds' of treatment. These rounds correspond to 30-day windows, and each animal was only present once in each round. The statistical aim of this observational study was to determine if there were important shifts in mean values over time. To answer this question, Shewhart control charts were created [32]. Control charts are a graphical way to determine if a process is in statistical control. Control limits are calculated as x-bar +/- 3s where x-bar is the overall mean and s is the standard deviation of measurements at each time point. If the mean goes outside of the control limits on the chart, it suggests that a mean shift has occurred and the process has a non-constant mean.

Adverse Effects

Adverse effects encountered during treatment that were documented in the medical record were noted and graded as mild, moderate, or severe. This grading scheme was adapted from the consensus document by the Veterinary Cooperative Oncology Group (VCOG) regarding standard terminology criteria for adverse events [33], correlating with Grade 1, 2, and 3 AE, respectively. As defined by VCOG, Grade 1 AEs included "asymptomatic or mild symptoms; clinical signs or diagnostic observations only; intervention not indicated." Grade 2 AEs were defined as "minimal, outpatient or non-invasive intervention indicated; moderate limitation of activities of daily living." Grade 3 AEs were defined as "severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; significantly limiting activities of daily living" [33]. Additionally, all documented non-hematologic AE were characterized as attributable to corticosteroids only, CA only, or to both drugs.

Results

Animals

Forty dogs met the inclusion criteria, comprising 24 spayed females, 2 intact females, 12 neutered males, and 2 intact males. The most common breeds represented were Maltese (7), mixed breed (6), Chihuahua (5), Yorkshire terrier (4), Golden Retriever (3), and French Bulldog (2); there were 1 each of the following breeds: Shiba Inu, Shetland Sheepdog, Schipperke, Boston terrier, Dachshund, Bichon Frise, Shih Tzu, Havanese, Boxer, Pug dog, Miniature Poodle, Siberian Husky, and Japanese Chin. The mean age at the time of diagnosis was 6.1 years (*SD* 3.1; range 8 months-13 years). Mean TNCC in the CSF was 278.1 (*SD* 425.6; range 5-1690). Mean CSF protein level was 151.9 mg/dL (*SD* 213, range 13-1168). The average duration of CA treatment was 18.25 months (*SD* 15.5, range 6-71), and a total of 743 CA doses were administered, comprising 735 SC treatments and 8 IV CRI treatments. Of these 743 doses, 539 were at a dosage of 400 mg/m^2, 129 were at a dosage of 200 mg/m^2, 71 were at a dosage of 300 mg/m^2, and 4 were at a dosage of 320 mg/m^2; the mean dosage was 318.5 mg/m^2 (*SD* 87.7, range 200-400 mg/m^2, median 400 mg/m^2, mode 400 mg/m^2). Treatments occurred initially every 3-4 weeks and, in some patients, were extended progressively longer based on clinical response and clinician preference. The mean time between treatment sessions was 31.8 days (*SD* 12.0, range 11-137). Corticosteroids administered included prednisone, prednisolone, and dexamethasone.

Hematologic Parameters

Mean values, standard deviation, and hospital reference range for RBCs, WBCs, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets in treated dogs are reported in Table 1. A total of 472 CBCs were performed with a median of 9 CBCs per patient (range 5-31). The mean

interval between CA treatment and CBC was 30.7 days (*SD* 15.5, range 1-134, median 28, mode 28). There were no statistically significant differences in the differential counts of RBCs, eosinophils, basophils, and platelets throughout the study, and there were no statistically significant cytopenias detected in any cell line. Total counts of WBCs, neutrophils, lymphocytes and monocytes showed infrequent sporadic statistically significant elevated values when compared to reference ranges. Of the 472 CBCs performed, 22 CBCs (4.87%) in five patients (12.5%) showed statistically significant elevation of at least one hematologic parameter over the course of the study. Three patients had a sporadic statistically significant elevation in total counts of WBC, neutrophils, and lymphocytes, and five patients had a sporadic statistically significant elevation in monocyte count. There was no statistically significant difference in the doses received by dogs who developed the elevations in hematologic parameters compared to those who did not, and none of the identified hematologic abnormalities precluded continued use of CA. The elevations in WBC and neutrophils (which occurred in the same three patients) first developed 3 weeks, 8.5 months, and 10 months into treatment. The elevations in lymphocytes first developed 8.5 months into treatment in two patients and 10 months into treatment in one patient. Finally, the elevations in monocytes first developed 3 weeks, 2 months, 8.5 months, 8.5 months, and 10 months into treatment. The elevations were noted on CBCs performed a mean of 20.2 days (*SD* 5.1) after the last CA treatment for WBCs, 19.8 days (*SD* 5.2) for neutrophils, 20.7 days (*SD* 4.2) for lymphocytes, and 21.9 days (*SD* 7.3) for monocytes.

Hematologic Parameters	Mean (x 10^3 uL)	Range (x 10^3 uL)	*SD*	Carolina Veterinary Specialists reference range (x 10^3 uL)	NC State University reference range (x 10^3 uL)	Number of patients with statistically significant abnormal hematologic values (and direction of abnormality)
RBC	6.153	3.47-8.77	0.875	5.10-8.50	5.68-8.8	0
WBC	12.881	4.4-83.4	7.86	6.0-17.0	4.36-11.9	3 (elevation)
Neutrophils	9.791	2.4-64.74	6.156	3.62-12.3	2.84-9.11	3 (elevation)
Lymphocytes	1.812	0.22-23.83	1.815	0.83-4.91	0.59-3.301	3 (elevation)
Monocytes	1.02	0.098-7.37	0.786	0.14-1.97	0.75-.85	5 (elevation)
Eosinophils	0.257	0-1.95	0.275	0.5-10.0	0.03-1.264	0
Basophils	0.038	0-0.53	0.048	0.0-0.12	0.0-0.192	0
Platelets	434.44	89-1294	157.29	117-490	190-468	0

Table 1: Mean values for hematologic parameters over course of treatment.

Of the 472 CBCs performed, no cytopenic values were observed for total WBC, neutrophil, monocyte, basophil, and eosinophil cell counts. There was a total of three isolated thrombocytopenias observed within three patients in the study. Two patients had a platelet count of 137,000 and 109,000 with observed clumping on manual cytology, and the third patient had a value of 114,000 platelets. No visual cytology was performed on this latter sample. There was a total of eighteen RBC values observed from nine patients that were below the institutions' reference range. Two of the nine patients had a low RBC value before any administration of cytarabine and steroids. Of the 18 low RBC values recorded, the mean and standard deviation were 4.63 +/- 0.33. There was a total of eight lymphopenias below the reference range in seven patients. Three of the seven patients had lymphopenia before administration of any cytarabine and steroids. Of the eight lymphopenias, the mean and standard deviations were 0.39 +/- 0.1. All nine of the dogs with low RBC values and two of the seven dogs with lymphopenia had a concurrent disease and/or were considered to be part of the AE population. These noted cytopenias did not achieve statistical significance.

Adverse effects potentially attributable to corticosteroids and CA therapy were reported in 10 patients throughout the study; they were mild in 5 patients, moderate in 3, and severe in 2. Adverse effects encountered in the study are outlined in Table 2. Nine dogs had an AE that could be secondary to either corticosteroids or corticosteroids in combination with CA, while only 1 dog had an AE (mild) directly attributable to cytarabine (transient lethargy and nausea post-injection).

Adverse effects (by patient)	AE attributable to steroids?	AE attributable to cytarabine?
Calcinosis cutis	Yes – mild	Yes – mild
1) Pancreatitis and elevated liver enzymes secondary to dietary indiscretion	Yes – moderate (pancreatitis) and mild (dermatitis)	Yes – mild (dermatitis)
2) Intermittent superficial dermatitis		
Alopecia and superficial dermatitis	Yes – mild	Yes – mild
1) Salivary gland abscess	Yes – moderate	Yes – moderate
2) Chronic dental disease causing submandibular lymph node enlargement and chronic hyperplastic ulcerative glossitis and cheilitis		
1) Lethargy and decreased appetite for 2-3 days after CA injection	No	Yes – mild
2) Vomited on the way home after one CA injection		
1) Anemia that resolved with gastric protectants	Yes – mild (dermatologic issues), moderate (anemia, cholecystitis, infections), and severe (infections)	Yes – severe (infections)
2) Dermatologic issues (peeling of pinnae, alopecia)		
3) Evidence of systemic infection on CBC (marked leukocytosis, neutrophilia with bands, lymphocytosis)-origin of infection not identified in the record; epistaxis; elevated liver enzymes		
4) Cholecystitis		
5) Multiple deep skin infections with draining tracts and bone exposure		
Intermittent diarrhea	Yes – mild	Yes – mild
Intermittent diarrhea and decreased appetite	Yes – mild	Yes – mild
1) Diarrhea - appeared to resolve with dietary management	Yes – moderate	Yes – moderate
2) Melena (presumptive GI ulcer)		
Severe hepatopathy	Yes – severe	Yes – severe

Table 2: Adverse effects, potential causes, and severity grading (adapted from VCOG) [33]
Legend: AE, adverse effects; VCOG, Veterinary Cooperative Oncology Group; CA, cytarabine

Discussion

Cytarabine serves as a promising secondary immunomodulatory drug in the treatment of MUE. However, current monitoring recommendations increase the financial burden owners undertake with this disease and may be unnecessary given the true incidence of cytopenias. Thus, we sought to investigate the hematologic parameters and AE in dogs treated long-term with CA for MUE, intending to develop more appropriate monitoring recommendations.

Results of the present study suggest that the use of corticosteroids and CA within a therapeutic range of 200-400mg/m^2 administered at a mean of every 31.8 days has infrequent effects on hematologic parameters and is safe with long-term use for treatment in dogs with MUE. No statistically significant cytopenias were detected, and only intermittent statistically significant elevated values were seen in total WBCs, neutrophils, lymphocytes, and monocytes. Furthermore, adverse effects were recorded in 10 patients, with only 1 patient displaying an AE that could be attributable only to CA rather than the combination of CA and corticosteroids.

Cytarabine is relatively rapidly cleared from the plasma by cytidine deaminase, though this process appears to be slower in dogs than in humans [26]. Its toxic side effects are dose-dependent in that at higher doses, the deamination reaction becomes saturated, leading to unpredictable increases in the plasma concentration of CA [16]. Traditionally, a biphasic leukocyte and neutrophil decline has been reported in people with the first nadir occurring at days 7-8 and the second occurring around days 20-24 [19,25]; however, more recently, a monophasic decrease was described with a nadir at day 10 or 14 depending on the dose

[16]. The nadir for thrombocytopenia has been reported to occur anywhere from 8-15 days [19-20,25].

While leukopenia (particularly neutropenia) and thrombocytopenia have been cited as AE, the majority of these studies are in humans, evaluate doses higher than what is traditionally used for MUE treatment, or involve co-administration with other chemotherapeutic drugs. Some of the earliest studies documenting these hematologic consequences were human studies performed by Burke, et al which revealed neutropenia, thrombocytopenia, and reticulocytopenia in patients treated with CA at variable doses (50-600 mg/m^2 and 1.0-1.2 mg/kg) [19,25]. Multiple studies since then have documented granulocytopenia/neutropenia and thrombocytopenia in people treated with repeated doses of CA ranging from (0.5-3 g/m^2) [16-17,27].

The veterinary literature has also documented similar evidence of myelosuppression. Thrombocytopenia and neutropenia have been reported in dogs treated with varying doses (150-600 mg/m2) of CA [20-24]. However, in all but one of these studies, CA was co-administered with other chemotherapeutic agents, including melphalan, L-asparaginase, vincristine, cyclophosphamide, doxorubicin, and carboplatin [21-24]. Only one study evaluated AE of CA as a sole chemotherapeutic agent in dogs and documented a mild thrombocytopenia in 50% of dogs that received a single 600 mg/m^2 IV bolus of CA [20]. This dose is notably higher than the doses used for MUE.

Several veterinary studies have previously attempted to evaluate the efficacy and safety of combined CA and corticosteroid treatment for MUE and have not identified evidence of significant myelosuppression [5-6,8,11-12,34]. However, most of these studies had small sample sizes (9 – 12 dogs) [5-6,8,12,34] or used CA doses lower than we report (100 mg/m2 to a maximum of 200 mg/m2)[5-6,8,11-12,34]. Lowrie et al. evaluated the safety and efficacy of CA (200 mg/m2 administered as a CRI or SC) in the largest cohort of dogs (80) with MUE treated with that drug to date; a statistically significant reduction in leukocytes and erythrocytes was noted in the CRI group compared to the SC group, but the values were still largely within the reference ranges [11]. In a recent study of 12 dogs, anemia was identified in 4 patients but could not be attributed solely to CA administration [34]. The findings of these studies provide support for the absence of statistically significant cytopenias documented in our study.

The infrequent, sporadically elevated values in some WBC counts in the present study are speculated to have been due to documented adverse effects of immunosuppressive treatment and possibly mild illnesses that were not overtly recognized by owners. As one example, intermittent elevations in WBCs, neutrophils, lymphocytes, and monocytes were seen in the patient with a salivary gland abscess and chronic dental disease (including hyperplastic ulcerative glossitis and cheilitis). Similarly, elevations in WBCs, neutrophils, and lymphocytes were documented in another patient with multiple recurrent infections (cholecystitis, deep skin infections with draining tracts).

It cannot be ruled out that the isolated lymphopenias and mild anemias noted could be attributed to concurrent steroid and cytarabine therapy; however, all nine of the dogs with low RBC values and two of the seven dogs with low lymphocyte values had a concurrent disease and/or were considered to be part of the AE population. Furthermore, the low RBC values accounted for only 3.8% of all CBCs while the lymphopenias accounted for only 1.7% of all CBCs, and they did not reach statistical significance.

Our study had several limitations. The retrospective nature prevented the standardization of CA dosages, as well as the frequency and timing of hematologic monitoring. Thus, it is possible that transient cytopenias were missed. Nonetheless, if undocumented cytopenias did occur, they were unlikely to result in relevant clinical disease necessitating medical intervention based on a review of the medical records and the absence of other major AE reported by owners. The retrospective study design could also lead to owner recall bias regarding AE (in particular, mild transient ones) given that most patients were only evaluated every 3 to 4 weeks.

Conclusion

The current standard is to monitor CBCs every 3 weeks or 1 week after treatment in patients receiving CA at 200 mg/m^2 [5,11,13]. However, the results of our study support a reduction in the frequency of CBC monitoring during MUE treatment with CA. We recommend that CBC monitoring be tailored to the individual patient and performed when the concern for a concurrent illness, such as an opportunistic infection, arises. This decreases the added cost and time associated with unnecessarily frequent monitoring while still allowing clinicians to periodically assess the health of a patient undergoing immunosuppressive treatment with chronic corticosteroid administration.

Conflict of Interest Statement

The authors have no conflict of interests to disclose.

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