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Evaluating the use of cytosine arabinoside for treatment for recurrent canine steroid-responsive meningitis-arteritis

Christian Günther ¹, Frank Steffen,¹ Daniela S Alder,^{1,2} Laura Beatrice,³ Caroline Geigy,^{3,4} Katrin Beckmann^{1,3}

Abstract

Background Relapses in steroid-responsive meningitis-arteritis (SRMA) are frequently observed but specific treatment protocols to address this problem are sparsely reported. Standard treatment includes prolonged administration of glucocorticoids as monotherapy or in combination with immunosuppressive drugs. The aim of this study was to assess the safety and efficacy of cytosine arabinoside (CA) in combination with glucocorticoids for treatment of SRMA relapses in 12 dogs on a retrospective basis.

Methods Dogs with recurrent episodes of SRMA and treated with a combination of CA and prednisolone were included. Information about clinical course, treatment response and adverse events was collected from medical records. Ethical approval was not required for this study.

Results Ten dogs (10/12) responded well to the treatment with clinical signs being completely controlled. One dog is in clinical remission, but still under treatment. One dog (8%) showed further relapse. Mean treatment period was 51 weeks. Adverse events of variable severity (grade 1–4/5) were documented in all dogs during treatment according to the veterinary cooperative oncology group grading. Three dogs developed severe adverse events. Laboratory findings showed marked changes up to grade 4. Diarrhoea and anaemia were the most often observed adverse events (6), followed by dermatitis (4), alopecia (3) and pneumonia (3). Including blood chemistry changes (13), 50 adverse events were found in total.

Conclusion Treatment with CA and glucocorticoids resulted in clinical remission in 10/12 dogs, but a high incidence of adverse events occurred requiring additional measures. All adverse events could be managed successfully in all cases.

Introduction

Steroid-responsive meningitis-arteritis (SRMA) is a well-recognised systemic inflammatory disease mainly

affecting young, medium to large breed dogs.¹ The acute form of SRMA is characterised by cervical rigidity, pain, pyrexia and a polymorphonuclear pleocytosis of the cerebrospinal fluid (CSF).^{2–4} There is no definitive antemortem diagnostic test for SRMA, but biomarkers and cytokines have been used to support the diagnosis and to understand the pathogenesis of SRMA.^{5–7} The precise aetiology of SRMA is still unknown. Immune-mediated mechanisms and dysregulated immune responses are suspected.² Standard treatment consists of prolonged administration of glucocorticoids, preferably prednisolone in stepwise tapering of dosage during approximately six months.⁸ In general, the prognosis for SRMA is good with relapses occurring in 16%–47.5%.^{9–11} A third of these cases suffer from more than one relapse.¹⁰ Possible reasons for relapses are inadequate dosage or duration of treatment.^{2,10}

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So far little is known about treatment of SRMA relapses. Adjusting glucocorticoids dosage and duration of treatment¹² or combining glucocorticoids with additional immunosuppressive drugs, for example azathioprine² or mycophenolate mofetil,⁸ have been described as therapeutic options, but studies investigating the efficacy and side effects are not sufficient.

Prolonged treatment with glucocorticoids has well-known side effects including diarrhoea, urinary incontinence, polyuria, polydipsia, cystitis, potbelly, alopecia, muscle atrophy, polyphagia, behaviour abnormalities, calcinosis cutis, gastric ulceration, thrombocytosis and thromboembolism.^{12–15} Especially large breed dogs seem to be prone to these side effects.¹⁶

In other canine non-infectious inflammatory diseases of the CNS such as meningoencephalitis of unknown origin (MUO) several studies have been published evaluating combinations of prednisolone with additional immunosuppressive drugs. Various combinations including cyclosporine, azathioprine, mycophenolate mofetil, cytosine arabinoside (CA), procarbazine, cyclophosphamide with vincristine, lomustine, leflunamide and radiation therapy have been described.^{17–22} No gold standard has been recommended. CA has been reported as an effective and well-tolerated treatment option with low costs for the treatment of MUO, but no data are available for its application in SRMA-relapse cases.¹⁷

The aim of this study was to assess the safety and efficacy of CA in combination with glucocorticoids in the treatment of SRMA relapses on a retrospective basis.

Material and methods

Case selection and medical records review

The medical records of the Veterinary Teaching Hospital of the University of Zurich were searched to identify dogs diagnosed with relapse of SRMA and treated with CA between 2011 and 2018.

Dogs were included if they had (1) complete medical records available; (2) clinical signs consistent with a relapse of SRMA (neck pain, hyperthermia and stiffness, leucocytosis, increased C reactive protein (CRP) in serum, CSF analysis with non-degenerated neutrophilic pleocytosis (reference interval:<5 white blood cells (WBCs/ μ L), negative analysis of infectious agents, initial response to glucocorticoid treatment) and (3) were treated for relapse with CA and prednisolone.

Dogs were excluded if medical records were not available, clinical signs were not consistent or if the relapse was not treated with CA.

Information obtained from medical records included signalment, duration of clinical signs before diagnosis, treatment received before relapse, general physical and neurological examination findings, and results of diagnostic tests including complete blood count, serum

biochemistry profile, ancillary tests for infectious agents and results of cisternal CSF analysis.

Due to the retrospective character no ethical approval was required for this study.

Treatment and follow-up

The specific treatment protocol was recorded for all dogs (glucocorticoid dosage, CA dosage, route of administration). Following admission, all dogs underwent at least one daily physical and neurological examination by a board-certified neurologist or a neurology resident. Neurological examination results and response to treatment (improvement, deterioration or static) were recorded in the medical records until discharge.

After discharge, medical records were searched for re-examination or owner/vet communication to confirm if the dog was alive or dead and to record the current treatment. For those dogs managed at their referring practices, the veterinary surgeon was contacted directly via telephone or email for an update on neurological status, treatment course and current treatment.

All documented adverse events were graded using the veterinary cooperative oncology group (VCOG) grading system. 'Grade 1: mild; asymptomatic or mild symptoms; clinical signs or diagnostic observations only; intervention not indicated. Grade 2: moderate; minimal, outpatient or non-invasive intervention indicated; moderate limitation of activities of daily living. Grade 3: severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; significantly limiting activities of daily living. Grade 4: life-threatening consequences; urgent interventions indicated. Grade 5: death related to adverse event'.²³

Results

A total of 57 dogs diagnosed with SRMA was identified between 2011 and 2018. Twenty of 57 dogs (35%) had recurrence of clinical signs. Median age of all dogs presented with SRMA was 10 months (range: 3–26 months).

Study population

Twelve dogs met the inclusion criteria. Six male dogs and six female dogs with relapses at a median age of 18.5 months (range: 12–29 months) and a median bodyweight of 29.0 kg (range: 8.4–50 kg) were included. Median age at initial clinical onset of SRMA was 8 months (range: 6–15 months). Represented breeds included three boxers, three Bernese mountain dogs, one mix-breed dog, one mastiff, one Coton de Tuléar, one Malinois and one Labrador retriever.

Initial clinical signs included hyperthermia, cervical pain with stiff gait and apathy without neurological deficits in all dogs. Following initial treatment with immunosuppressive dosages of prednisolone eight dogs

showed signs of relapse while still under treatment. The dogs were pretreated with prednisolone for a median time of 7 months (range: 1–12 months).

Four dogs (4/12) developed clinical signs 4–10 months after cessation of the initial treatment protocol (mean disease-free interval: 7 months). At the time of relapse, the dogs were presented with neck pain (10/12), apathy (4/12), anorexia (2/12) and hyperthermia (7/12). No neurological deficits were found.

For 11/12 dogs, prednisolone monotherapy was the only treatment before initiation of CA with prednisolone. One dog had two relapses of SRMA before CA treatment was started. The first recurrence was treated with prednisolone only, but because of severe side effects, one month after initiation of prednisolone treatment, azathioprine was added in order to reduce prednisolone dosage. Four months after initiation of azathioprine a second relapse occurred under a prednisolone dosage of 0.5 mg/kg every 12 hours and azathioprine 2 mg/kg every 48 hours. Additionally, the dog had developed a marked increase of alanine transaminase, alkaline phosphatase and aspartate transaminase.

Laboratory findings

Initially CRP was measured in five dogs, the median CRP level was 137 mg/L (range: 0.4–257 mg/L) in serum. CSF analysis in all dogs revealed a non-degenerated neutrophilic pleocytosis with a median nucleated cell count of 18.9/μl (range: 0.67–3765 /μl) and a median protein content of 0.15 g/L (range: 0.09–2.08 g/L).

Haematology at the time of relapse revealed leucocytosis in 11 of 12 dogs, mainly with neutrophilic granulocytosis combined with monocytosis in 4 dogs. CRP was measured in seven dogs and ranged from 0.7 to 137 mg/L (median: 73 mg/L). CSF analysis was available in 11 dogs. In 10 dogs non-degenerated neutrophilic pleocytosis was present. In one dog the CSF was normal. Leucocyte count ranged from 0 /μl to 597 /μl (median: 42 /μl). Median CSF protein content was 0.22 g/L (range: 0.09–0.47 g/L).

Treatment

Treatment with prednisolone and CA was initiated if relapse occurred during or after prednisolone monotherapy or during prednisolone and azathioprine treatment.

Until April 2014 dogs (n=4) were treated with subcutaneous injections of CA (Cytosar, Pfizer PFE Switzerland, Zurich, Switzerland; 50 mg/m² every 12 hours for two consecutive days). Later, dogs (n=6) received CA as a constant rate of intravenous infusion during eight hours with a dosage of 25 mg/m²/hour, based upon a modification of the protocol by Lowrie *et al.*²⁴ In the present investigation, the treatment protocol was shortened to three administrations every three weeks, followed by three administrations every four weeks. Afterwards three administrations every five

Table 1 Grades and numbers of specific adverse events

CTCAE grade Type of adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhoea		6	1		
Colitis			1		
Otitis externa		2			
Pyelonephritis			1		
Dermatitis (all types)		4			
Cystitis		2			
Alopecia	3				
Polyuria	1				
Polydipsia	1				
Autoimmune disorders			1 (ITP)		
Pneumonia			3		
Fever	2	1			
Hyperpigmentation	1				
Anaemia	6	1			
Alkaline phosphatase	1	2		2	
ALT		1	1	1	
Lipase	1		1	1	
Bilirubin	1	1			

Further diseases not classified: calcinosis cutis, lymphocytopenia, pyogranulomatous lymphadenitis. ALT, alanine aminotransferase; CTCAE, common terminology criteria for adverse events; ITP, immune-mediated thrombocytopenia.

weeks and finally three administrations every six weeks were applied.

In one dog a total of eight administrations was given because of owner's preference. Median treatment time period was 10 months (range: 8.5–12.5 months) with a median of 12 CA administrations (range: 8–14 administrations).

Additionally, the dogs received prednisolone (Prednisolon, Streuli Pharma AG, Uznach, Switzerland) following the protocol described by Cizinauskas *et al.*⁸ Starting with an initial dosage of 4 mg/kg per day for two days, followed by 2 mg/kg per day for two weeks and afterwards 1 mg/kg for four weeks. Further dosage was tapered over a total of six months, depending on the clinical response and severity of side effects noted during treatment.

Response to treatment and adverse events

All owners reported a fast response within the first days of treatment. At the recheck three weeks after initiation of CA all patients showed complete resolution of clinical signs of SRMA.

Adverse events

Adverse events are summarised in [tables 1 and 2](#).

Overall the grades ranged from 1 and 4. Three dogs developed severe adverse events requiring intensive and prolonged medical treatment. Grade 4 was recorded in laboratory findings only.

In total 50 adverse events were noted, 26 in the subcutaneous treated dogs and 24 in the intravenously treated ones. In both treatment protocols grade 4 was observed in laboratory findings only.

Table 2 Listing of each patient with its adverse events

No	Breed	Age at relapse, months	Sex	Weight (kg)	Adverse events: VCOG-CTCAE grade (in brackets)	Further diseases while treatment	CA protocol
1	Boxer	29	M	37.0	Diarrhoea (2), pyoderma (2), anaemia (1)	None	SC
2	Boxer	14	M	26.5	Diarrhoea (2), otitis externa (2), anaemia (1)	None	IV
3	Boxer	15	W	25.7	Anaemia (1)	None	SC
4	Mastiff	13	M	50.0	Pyelonephritis (3), bacterial cystitis (2), calcinosis cutis, dermatitis (2), lymphocytopenia, otitis externa (2), fever (1), AP (4), ALT (4), BUN (2), anaemia (2)	Two foreign bodies	SC
5	Bernese mountain dog	27	Wk	35.0	Diarrhoea (2), bacterial cystitis (2)	None	SC
6	Mix-breed dog	21	M	19.5	Dermatophytosis (2)	None	IV
7	Bernese Mountain dog	24	W	32.4	Diarrhoea (2), alopecia (1), polyuria (1), polydipsia (1), immune-mediated thrombocytopenia (3)	None	SC
8	Coton de Tuléar	12	M	8.4	None	None	IV
9	Malinois	24	M	28.0	Diarrhoea (2), anaemia (1) pyogranulomatous lymphadenitis	None	IV
10	Bernese mountain dog	18	Wk	35.6	Diarrhoea (3), colitis (3), parasitic pneumonia (3), fever (1), fever (2), hyperpigmentation (1), AP (4), lipase (4), ALT (3), BUN (1), anaemia (1)	Stomach distention after excessive food intake	IV
11	Bernese mountain dog	12	W	30.0	Diarrhoea (2), dermatitis (2), parasitic pneumonia (3), alopecia (1), AP (1), anaemia (1)	None	SC
12	Labrador retriever	19	W	20.6	Bacterial pneumonia (3), alopecia (1), AP (2)	None	IV

ALT, alanine aminotransferase; AP, alkaline phosphatase; BUN, blood urea nitrogen; CA, cytosine arabinoside; CTCAE, common terminology criteria for adverse events; IV, intravenous; M, male entire; SC, subcutaneous; VCOG, veterinary cooperative oncology group; W, female entire; WK, female neutered.

Follow-up

The median follow-up was 27 months (range: 6–60 months). One dog is still under treatment, receiving its tenth CA administration. One dog was lost to follow-up after finishing the CA protocol.

Follow up haematology, serum biochemistry profiles and/or serum CRP measurements were performed in an individual fashion based on the clinical status of the dog. Haematology was performed before the second administration of CA in all dogs. In six dogs haematology was repeated monthly. In seven dogs the haematocrit dropped below the reference value (<42%) after the first administrations but recovered during treatment course.

Seven months after finishing a shortened protocol with just eight administrations one dog showed a relapse with fever, stiffness and neck pain after movement. This dog had received CA intravenously.

No neurological deficits were found. The protocol was started again with prednisolone at a dosage of 2 mg/kg every 24 hours orally and 1 mg/kg azathioprine every 48 hours orally. The dog showed remission of clinical signs and no further relapse occurred yet.

In the remaining dogs the clinical signs were controlled completely and no signs of SRMA recurred during the observation period. Available follow-up bloodwork of 8/12 revealed normal CRP concentrations and normal haematology findings.

Outcome

Ten dogs were alive at the time of publication. One dog was lost to follow-up after finishing the protocol and one dog was euthanased due to an alveolar carcinoma 24 months after cessation of the treatment protocol.

This dog was diagnosed with immune-mediated thrombocytopenia six weeks before finishing CA protocol and received a tapering dosage of prednisolone for 18 months.

Discussion

Reports on treatment of recurrence of SRMA are sparse. This study describes a series of 12 dogs with SRMA relapse treated with CA and prednisolone with respect to response to therapy, adverse events treatment and long-term outcome.

Initially, dogs with SRMA respond well to treatment with glucocorticoids. However, the rate of relapse is reportedly high and ranges between 16% to 47.5%.^{4,10–12} Relapses have been attributed to inadequate dosage or duration of treatment.^{2,10} Individual insensitivity to glucocorticoids may represent an alternative explanation for insufficient response to treatment. Glucocorticoid insensitivity has been described in people with asthma and other chronic inflammatory diseases.^{25,26} An insensitivity caused by interleukin (IL)-17/23 is described by Vazquez-Tello *et al.*²⁷ Interestingly, in human medicine the non-responding rate in chronic inflammatory diseases is 20%–30%,^{26,28} which resembles the rate of relapses in canine SRMA. Reports about glucocorticoid insensitivity in chronic inflammatory diseases in dogs are lacking, but possible mechanisms have been examined in healthy dogs and discussed as a hypothetical explanation in dogs with recurring inflammatory bowel disease.^{29,30}

In several other immune-mediated diseases such as immune-mediated thrombocytopenia, anaemia, dermatological diseases and enteropathies, a combination of immunosuppressive drugs improve

outcome.^{31 32} Similar to SRMA, combinations of immunosuppressive drugs do not represent a gold standard but are reported to be associated with less side effects compared with glucocorticoid monotherapy.^{33–35}

The treatment of SRMA relapse can be frustrating. Poor response, several relapses or complications associated with medication for SRMA can even lead to euthanasia in severe cases. No reliable predictive indicator exists for relapse-free successful therapy.^{8 10}

Few data on how to manage SRMA relapses are available. Increasing prednisolone dosage and continuing the prednisolone protocol for a six-month duration resulted in complete remission of clinical signs in all dogs in one study, but in 25% (1/4 dogs) a second relapse was documented. Reported adverse effects in this study included diarrhoea (14/20), polyuria and polydipsia (13/20), weight gain (10/20) and polyphagia (6/20).¹² In another study relapse was addressed by increasing the prednisolone dosage, but in 40% (4/10) of the cases this was not sufficient to control clinical signs and a second immunosuppressive drug was added (20 mg/kg mycophenolate mofetil every 48 hours). Reported side effects with this protocol included polyuria/polydipsia (7/9), polyphagia and obesity (6/9), urinary tract infection (3/9), vomiting/diarrhoea (2/9).⁸ A study from North America describing the clinical course of SRMA stated the use of several second immunosuppressive drugs in 44.8% of dogs which showed a relapse. But no specific distinction of the glucocorticoid monotherapy and combined therapy was made.¹¹

In the present investigation, CA was chosen as an add-on treatment, because it has been successfully applied in dogs with MUO. It is associated with mild to hardly any adverse events and is relatively low in price.

CA is a synthetic nucleoside, a pyrimidine analogue acting as an anti-metabolite. It is incorporated into the DNA as a false nucleoside component, leading to impaired DNA synthesis and cell death. CA penetrates the blood-brain barrier and if administered intravenously as a constant rate infusion it reaches a significant concentration in CSF.³⁶

In the present investigation, all dogs treated with prednisolone and CA showed remission of clinical signs of SRMA within the first weeks following the first administration of CA. However, this effect could also be attributed to the concomitant increase in dosage of prednisone. While Lowrie *et al* reported complete remission with increased dosage of prednisolone,¹² this was insufficient in 40% of cases reported by Cizinauskas *et al* necessitating the need for a second immunosuppressive drug.⁸

Successful outcome with no further relapse during a median follow-up time of 27 months was achieved in 10/12 dogs (80%). Only in one dog (8%) another SRMA relapse was diagnosed eight months after cessation of a shortened CA protocol. This dog was treated with

an increased dosage of prednisolone in combination with azathioprine. As this is the only dog in this series receiving a shortened protocol it is unclear if prolonged treatment with CA could have prevented this relapse. Furthermore, neither serum CRP nor CSF has been monitored in this dog. And also, relapses have been reported in dogs with normal serum CRP and CSF.¹⁰ It is unclear if incomplete control of the inflammation could have been identified using these methods and therefore guiding towards prolonged treatment.

None of the dogs developed neurological deficits as described previously in chronic cases of SRMA.⁴

Because CA is a chemotherapeutic drug, complications during therapy were recorded according to the common terminology criteria for adverse events used in veterinary oncology (VCOG-CTCAE). This includes reporting of all unfavourable and unintended signs (including abnormal clinicopathological findings), clinical signs or disorders temporally associated with the use of an anti-neoplastic agent that may or may not be considered related to the drug administration. While this allows a detailed description of events associated with the medication, it does not necessarily indicate that they are solely attributed to CA administration. All dogs received prednisolone together with CA and many of the documented adverse effects including diarrhoea, polyuria/polydipsia, urinary tract infection, alopecia/hyperpigmentation have been observed at similar rates in long-term follow-up studies of SRMA cases receiving prednisolone¹² or with prednisolone and mycophenolate⁸ indicating that these adverse events are most likely attributed to prednisolone treatment. Transient mild anaemia has been reported in dogs with MUO treated with CA and this was also detected in 7/12 dogs in this study suggesting a possible association with CA administration.²⁴

Other adverse events such as pneumonia secondary to *Angiostrongylus vasorum* infection may be related to insufficient immunoreaction due to prednisolone and/or CA treatment, but in endemic areas this may also reflect insufficient parasitic prophylaxis.

Another interesting finding of this study was the presence of additional immune-mediated diseases in 6/12 dogs (50%) including atopic dermatitis (5/12) and immune-mediated thrombocytopenia (1/12).

The use of CA and prednisolone in dogs with MUO was associated with mild side effects only. In contrast, adverse effects were observed more frequently and were more severe in the present investigation. There are several hypotheses to explain this difference. While MUO is restricted to the CNS, SRMA has a more systemic nature and the immune system in general seems to be dysregulated. Another explanation may be the signalment of dogs with SRMA that are substantially larger (median bodyweight of 29 kg in the present study) compared with dogs with MUO (typically small breed dogs). In large breed dogs different pharmacokinetics

of steroids may result in more clinically relevant side effects.³⁷ Possibly using the body surface as a basis for the calculation of the prednisolone dosage instead of the bodyweight, some of the side effects could be reduced as suggested in a recent publication.³⁷ A third reason might be different reporting schemes: while in the present study all clinical and laboratory abnormalities were reported during treatment, previous studies mainly included adverse events clearly related to the administration of CA.

In one recent study the VCOG grading system was applied, but only to the haematological abnormalities.³⁸ Post-treatment haematology changes ranging from grade 1 to grade 2 were found in 4/49 (8%) samples in MUO cases.³⁸ In contrast 17/56 (30%) grade 1 abnormalities in the samples of the dogs with SRMA included in the present study were identified, supporting higher incidence of adverse events in dogs with SRMA compared with dogs with MUO.

However, a greater understanding of the immunopathogenesis of SRMA may lead to alternative treatment options with less side effects in this common but still not adequately controlled disorder. Investigating the cytokine pathways^{36 39 40} and influence of the endocannabinoid system on the inflammatory response in dogs with SRMA,⁴¹ a dysregulation of several cytokines including IL-23 and IL-17 was found. These two cytokines seem to play a major role in SRMA, and in other immune-mediated diseases in dogs such as inflammatory bowel disease, asthma and chronic inflammatory arthritis.^{42–44} These data indicate the need of further research in the area of immune-mediated diseases in dogs and their management.

Limitations of this study are primarily related to its retrospective character, the small study population, absence of a control group and the use of two different routes of CA administration. A prospective randomised study design using different treatment protocols would be necessary to eliminate flaws and biases and to compare safety and efficacy of different treatment protocols in order to provide more robust results. Based upon the benefit and relative safety of the presented treatment protocol it can be recommended as management for SRMA relapses until more evidence-based studies are available.

In the present study SRMA relapses were successfully controlled in all dogs and further relapses were prevented in 11/12 dogs. None of the dogs were euthanased or died because of the disease or complications associated with treatment. However, in all dogs, adverse events in various degrees of severity were observed. Based upon these results, this treatment protocol can be recommended as an effective treatment option but monitoring of the patients is required to recognise and control adverse events.

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