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Cytosine arabinoside constant rate infusion without subsequent subcutaneous injections for the treatment of dogs with meningoencephalomyelitis of unknown origin

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ABSTRACT

Background: The administration of cytosine arabinoside (CA) by continuous rate infusion (CRI) at time of diagnosis has been shown to improve the 3-month survival of dogs diagnosed with meningoencephalomyelitis of unknown origin (MUO), compared to subcutaneous (SC) administration. The benefit of administering subsequent sequential CA SC injections is unknown. This study compares the outcomes of a CA CRI protocol with (CRI + SC group) or without (CRI group) follow-up CA SC injections; both groups received adjunctive prednisolone.

Methods: Forty-two dogs diagnosed with MUO were recruited (CRI group) and compared with 41 historical control dogs (CRI + SC group) in a prospective, controlled clinical trial with 36 months follow-up.

Results: Success rates were respectively 64.3% and 65% in the CRI and the CRI + SC groups at 40 weeks following diagnosis, and 32.5% and 35.9% at 36 months following diagnosis. Median time to relapse was 299 and 285 days for the CRI and the CRI + SC groups respectively. No statistical significant difference was found ($p \geq 0.05$).

Conclusion: No clear benefit was identified in the administration of subsequent sequential CA SC injections after the first administration of CA by CRI for the treatment of dogs diagnosed with MUO.

Key words: cytarabine, cytosar, meningoencephalomyelitis of unknown (a)etiology, granulomatous meningoencephalomyelitis, necrotizing meningoencephalomyelitis, necrotizing leukoencephalitis

INTRODUCTION

Meningoencephalomyelitis of unknown origin is a group of idiopathic, inflammatory central nervous system diseases of presumed immune-mediated origin, encompassing granulomatous meningoencephalomyelitis (GME), necrotizing meningoencephalomyelitis (NME) and necrotizing leukoencephalitis (NLE). This group of diseases is considered fatal if left untreated, but no consensus has yet been reached on the ideal treatment protocol of these dogs. Glucocorticoids are generally considered to be the mainstay of treatment, often in combination with additional immunosuppressive drugs.[1] A popular treatment protocol for dogs diagnosed with MUO is the combination of CA with glucocorticoids tapered slowly over several months[2-5]. A clear improvement in survival at 3 months following diagnosis has been shown with the administration of CA at the time of diagnosis by CRI compared to SC delivery[6]. In this treatment protocol, subsequent SC CA injections are performed every few weeks (initially at 3-week intervals, and then less and less frequently over time) following the CRI for a total duration of 72 weeks (18 months). Because of the extended duration of the therapeutic regime and the 48 hour hospitalisation required for each cycle of CA therapy, this treatment protocol requires considerable time and financial commitment from the owner. The aim of this study was to assess the necessity of administering subsequent SC CA injections for the treatment of dogs with MUO following a single CRI of CA, by comparing the clinical outcome in a cohort of dogs receiving initial CA CRI without further regular cycles of CA with historical control data. Further outcome data is also presented from the historical control group.

MATERIALS AND METHODS

Dogs

This study adds to data from a previous prospective treatment trial of the effect of oral prednisolone and CA administered by CRI followed by SC injections in dogs with MUO. Complete details of this study are described elsewhere.[5,6] Dogs with MUO presented consecutively at the neurology department of Davies Veterinary Specialists between August 2011 and August 2015 were recruited prospectively to form the CRI + SC.[6] Dogs presented consecutively at the neurology department of Dovecote Veterinary Hospital between August 2015 and July 2017 were then recruited prospectively to form the CRI treatment group. For both groups, following receipt of owner consent, dogs with a history of steroid administration prior to presentation were excluded from the study. Signalment and history were recorded, including the duration of clinical signs before investigations. Physical and neurological examinations were performed. Blood analysis including complete blood count, biochemistry, antibody titers to *Neospora caninum* and *Toxoplasma gondii* (indirect fluorescence antibody tests), MRI of the brain (0.4T magnet [Aperto MRI, Hitachi, Tokyo, Japan] for the CRI + SC group and 0.25T permanent magnet [Esaote VetMR Grande, Genova, Italy] for the CRI group) and cerebrospinal fluid (CSF) analysis (including a total nucleated cell count (TNCC), cytology and protein concentration) were also performed. Dogs were followed-up prospectively for at least 36 months following diagnosis and initiation of treatment.

Diagnosis

A presumptive diagnosis of MUO was based on guidelines of a previous study[7]. Dogs were considered to have MUO if they were older than 6 months, with evidence of single, multiple or diffuse intracranial abnormalities on MRI, CSF pleocytosis (TNCC > 5 cells/µL, erythrocyte count < 4000 cells/µL), > 50% mononuclear cells and an absence of antibodies against *Neospora caninum* and *Toxoplasma gondii*. Dogs with focal cortical abnormalities that appeared hypo-intense on T1-weighted images were excluded from the study (given this

may represent a necrotizing form of MUO), as were those with the optic focal form of GME. The presence or absence of MRI features as single or multiple abnormalities, sulci effacement, rostral and/or caudal fossa involvement, contrast enhancement, mass effect, foramen magnum and/or trans-tentorial herniation were also determined for each case. Diagnosis for a relapse was made based on recurrence of initial clinical signs and when possible, repeated MRI of the brain and CSF analysis.

Treatment

All dogs were treated with a standard protocol of prednisolone, starting at immunosuppressive doses and then tapering progressively over 34 weeks, as well as an initial CRI of CA at the dose of 100mg/m^2. The first 41 dogs then continued to receive sequential SC injections of CA at a dose of 50mg/m^2 every 12h for 2 days (CRI + SC group), initially at 3-week intervals and then at a decreasing frequency for a total of 72 weeks (18 months), the 3-month survival outcome in this group has been reported previously[6]. The remaining 42 dogs did not receive any further CA administration (CRI group). Both treatment protocols are outlined in Figure 1. If a dog relapsed at any point during this treatment scheme, decisions on treatment were altered on an individual basis. As this was an accessional study, any dog with a diagnosis of MUO was immediately assigned to the CRI group and included in the results analysis, even if the CRI was unable to be commenced or completed (e.g. due to death).

Outcome

Treatment “success” was defined as sustained neurological improvement following initiation and completion of the standardized treatment protocol. All dogs with signs suggestive for recurrence or persistence of signs necessitating a change in the treatment plan were termed as “relapse”, including dogs that needed a long-term very small dose of prednisolone to manage

their clinical signs and achieve sustained remission. All dogs that died or were euthanized following diagnosis were termed “dead” and included in the statistics and survival analysis.

Primary outcome measures were the success, relapse and death rates for each treatment group. Those were assessed at 4 different timespans: at 34 weeks (completion of prednisolone treatment protocol), 40 weeks (6 weeks after prednisolone discontinuation), 72 weeks (end of the SC CA injections for the CRI + SC group) and 36 months following diagnosis. Repeat MRI and CSF were also performed at 3 months following diagnosis in 37/41 dogs of the CRI + SC group and 36/42 dogs of the CRI group.

Time to relapse was assessed as a secondary outcome measure over the 36-month study period. Median survival times were determined for the entire group of dogs and for the subset of dogs that could be followed up until death (related or not to MUO).

Statistical analysis

Baseline characteristics of dogs in the 2 groups were compared: categorical variables (sex, MRI features) were compared using a Fisher exact test, whereas continuous variables (age, delay to presentation, CSF TNCC, CSF protein concentration) were compared using a Mann-Whitney test. Primary outcome measures were compared between both groups using a Fisher exact test, whereas time to relapse was compared using a Mann-Whitney test. Long-term survival analysis (> 36 months) was assessed with a Kaplan Meier survival curve as well as a log rank analysis. Statistical significance for all tests was set at $\alpha < 0.05$.

RESULTS

Patients

A total of 83 dogs were recruited. Forty-one dogs were given sequential CA SC injections after the initial CA CRI (CRI + SC group) and acted as historical controls, a further 42 dogs were recruited prospectively and did not receive any CA injections following the initial CA CRI (CRI group). There was no significant difference in age at presentation, sex, delay to presentation or CSF analysis between the two groups (Table 1). As it has been shown previously that some MRI features at the time of diagnosis can have an impact on mortality[5,6], these features were also compared and no significant difference was found between groups (Supplementary information files). Over the 36-month study period, 2 dogs from each group were lost to follow-up, at 270 and 472 days for the CRI + SC group and at 301 and 372 days for the CRI group. Those dogs were doing well at the time they were lost to follow-up, but were removed from the study calculations and statistics at their respective time points when lost to follow-up in order to avoid bias. Sample size therefore decreased to 40 dogs at 40 weeks and 39 dogs at 72 weeks for the CRI + SC group, and 40 dogs at 72 weeks for the CRI group and remained constant thereafter until 36 months (Table 2).

Primary outcome measures: success, relapse and death rates

At 34 weeks (238 days), treatment success was seen in 28/42 dogs (66.7%) in the CRI group, and in 31/41 dogs (75.6%) in the CRI + SC group. Relapse was seen in 8 dogs (19%) in the CRI group and in 6 dogs (14.6%) in the CRI + SC group. Six dogs (14.3%) in the CRI group and 4 dogs (9.8%) in the CRI + SC group died as a consequence of their MUO. At 40 weeks (280 days), success rates reduced to 64.3% and 65% (27/42 and 26/40 dogs), and relapse rates were 21.4% and 25% (9/42 and 10/40 dogs) for the CRI and CRI + SC groups respectively. At 72 weeks (505 days), treatment success further decreased to 45% and 43.6% (18/40 and 17/39) of dogs and relapse increased to 40% and 46.1% (16/40 and 18/39) of dogs in the CRI and the CRI + SC groups respectively. At 36 months (1095 days) following diagnosis, success

rates decreased to 32.5% and 35.9% (13/40 and 14/39 dogs), whereas 52.5% and 53.8% (21/40 and 21/39) of dogs had relapsed for the CRI and the CRI + SC groups respectively. All these values were compared and found not to be significantly different ($p \geq 0.05$; Table 3). The last two dogs died between 5 to 6 months after diagnosis, so all dogs that were alive 6 months (24 weeks) following diagnosis, (85% of dogs from the CRI group and 89.7% of dogs from the CRI + SC group) remained alive 36 months following diagnosis. No adverse effects were reported by owners.

MRI and CSF abnormalities at three month follow-up were collected. Thirty-four of 37 (92%) surviving dogs in the CRI+ SC group had a normal MRI scan at 3 months, compared with 32/36 (89%) surviving dogs in the CRI group (P = 0.71). In addition, CSF was normal in a similar proportion of dogs from each group (36/37 dogs in CA + SC, 97% versus 34/36 dogs in CRI, 94%; P = 0.61).

Secondary outcome measures: time to relapse and survival times

Median time to relapse was 299 days (range: 82-1024 days) for the CRI group and 285 days (range: 97-1081 days) for the CRI + SC group ($p = 0.88$). At 36 months, 21 dogs from each group were receiving a long-term low dose of prednisolone in order to maintain remission of clinical signs, which represented 61.8% of the surviving population in the CRI group, and 60% of the surviving population in the CRI + SC group.

A Kaplan Meier survival curve was generated to assess long-term survival (Figure 2). In total, 16/42 dogs (38.1%) from the CRI group and 15/41 dogs (36.6%) from the CRI + SC could be followed long-term until their death (whether related to their MUO or not); the remaining dogs being either alive or lost to follow-up. Median survival time of deceased dogs was 1131

days (range: 0-2081 days) for the CRI group and 1745 days (range 0-3045 days) for the CRI + SC group. This was not significantly different ($p = 0.17$). As ≥ 85% of the dogs (34/40 dogs in the CRI group and 35/39 dogs in the CRI + SC group) were still alive at the end of the study (36 months), the median survival time could not be assessed in either of the two groups, but as the median follow-up time in both groups was >1095 days, the median survival time will be at least as long.

DISCUSSION

In this study, no significant difference was found in the medium to long-term outcome of dogs with MUO treated with an initial CA CRI with or without sequential follow-up CA SC injections. Even though a small difference in the success and relapse rates seemed to be present between both treatment protocols at 34 weeks, those rates became equivocal at 40 weeks until 36 months following diagnosis (Table 3). Median time to relapse was also comparable between both groups about 10 months following diagnosis, shortly after discontinuation of prednisolone therapy. About 85% of dogs in the CRI group and 90% of dogs in the CRI + SC group were alive and well at 36 months following diagnosis (the end point of this study), but ≥60% of dogs in both groups had to receive a small dose of prednisolone indefinitely to maintain remission. This raises the question of whether MUO dogs might benefit from receiving a very small dose of prednisolone in the longer-term instead of discontinuing at 34 weeks, but our study has not addressed this hypothesis. Relapse as a consequence of prednisolone dose reduction or withdrawal has been reported previously in 2 dogs[4]. One dog in this same study was found to relapse after discontinuation of the CA SC injections. None of the dogs in our study were found to relapse or die shortly after discontinuation of the CA SC injections.

Ten dogs from this study died from their MUO: 6 dogs from the CRI group and 4 dogs in the CRI + SC group. It is important to note that 8 of these dogs (4 from each group, 10%) died within the first 5 days following diagnosis, which is in accordance to the previously reported finding that about 15% of dogs with MUO die shortly following diagnosis[7,8]. Two previous studies[5,9] reported 33% and 26% of dogs died within 1 week of MUO diagnosis respectively, which is higher than the 1-week mortality rate of our study. A possible explanation is the exclusion of cases with hypointense lesions on the MRI (suggestive of necrotizing encephalitis) in our study, whereas these cases were included in the study by Cornelis et al[9]. These studies also have different treatment protocols with the main variance being the standardised delivery of CA via a CRI in the present study, something that has been shown to be superior[6], versus the heterogeneous regime in the earlier papers consisting of prednisolone with subcutaneous CA[5] or a combination of prednisolone with or without CA delivered predominantly subcutaneously. The remaining 2 dogs that died during the 36-month period of observation did so between 5 and 6 months following diagnosis. Spontaneous death in cases diagnosed with MUO might be due to progression of the disease with involvement of the brain[1], and therefore likely represents an extremely aggressive form of relapse. All 10 dogs that died had multiple brain lesions, mass effect and trans-tentorial herniation, 9 had sulci effacement and 4 (3 from the CRI group and 1 from the CRI + SC group) had foramen magnum herniation at time of diagnosis. Those MRI findings have been identified as risk factors predicting mortality[5,8]. There was no statistical difference in the number of dogs with multiple brain abnormalities, sulci effacement, mass effect or foramen magnum herniation between the CRI and the CRI + SC groups. All dogs with available follow-up that were alive at 6 months remained alive at 36 months (1095 days).

Several studies describe the use of a combination of CA and prednisolone for the treatment of dogs with MUO[2-4,10]. However, only one of those studies describes the use of a single CA CRI combined with prednisolone in 9 dogs[10]. A median survival time of 1063 days was reported in that study, which is similar to the median survival of the deceased dogs from our CRI group (1131 days), and similar or inferior to the median survival time of all our dogs (> 1095 days). It is important to note that our median survival time of 1131 days is based only on the dogs that were followed until death (related to their MUO or not). Subsequently this likely underestimates the true median survival time of the dogs in our study if the observation period had been extended until the time of death of all dogs. Overall, these figures are comparable to the 26-1025 days median survival times found in the literature for various protocols combining prednisolone and CA[1-6].

CA CRI has been shown to be both pharmacokinetically[12] and clinically[6] superior to SC administration, due to the achievement of a consistent and prolonged plasma steady-state concentration believed to allow better CNS penetration of the drug[6,10,12]. CA is considered to be a safe therapy in dogs with MUO, with only minimal adverse effects reported in previous studies[2-6,10]. Localised alopecia, dermatitis, calcinosis cutis and deep pyoderma have been described in rare cases with the SC route of administration of CA[3,13], whereas gastrointestinal toxicity and myelosuppression are more common with high doses (300-600mg/m^2) of CA administered by CRI[14,15]. No adverse effects have been reported following a single CA CRI at the dose of 100-200mg/m^2 [6,10-12], which was also observed in the dogs of our study.

One of the major limitations of this study is that none of the cases were histopathologically confirmed. We decided not to use post-mortem or invasive biopsy as a requirement for inclusion, as this could have confounded our results by selecting dogs with a poorer outcome,

either because they died, or by performing an invasive biopsy which could increase the risks of morbidity and mortality. Consent for post-mortem analysis could unfortunately not be obtained for any of the dogs that died in this study. Second, the diagnosis of relapse was mainly based on the recurrence of clinical signs and response to treatment adaptation, with only a minority of dogs having a second MRI or CSF analysis to confirm. Even though response to treatment was seen in all cases, this argument cannot be used to confirm the suspected relapse due to the large spectrum of action of the prednisolone; therefore, some of the dogs termed as "relapses" may in reality have been suffering from a separate condition rather than having a true relapse. A third limitation includes the survival analysis, as not all dogs included in the Kaplan Meier curve died from their MUO as they often already had an advanced age. Finally, this study was neither blinded nor randomized, and the treatment protocols were performed at different time points. However, all other variables of this study were kept constant to minimize inaccuracies in the study results, and as both groups did not differ significantly in any of the criteria at the starting point, we are relatively confident that potential biases are limited. The one exception to this was the field strength of the MRI altered between groups but both magnets were low-field and this may have excluded the more mildly affected dogs from the CRI only group by failing to identify lesions on the MRI and hence artificially improve this treatment modality. However, the similarity of outcome with both treatment modalities would suggest this would not alter our conclusion.

CONCLUSION

This study did not show a significant difference in the medium to long-term prognosis of dogs with MUO treated with an initial CA CRI and adjunctive prednisolone protocol with or without sequential follow-up CA SC injections. The proposed treatment protocol is less time consuming and expensive, which could lead to improved owner compliance. The majority of

283 dogs appear to relapse, most of them shortly after discontinuation of the prednisolone,
284 necessitating the need to resume this medication and maintaining a small long-term dosage to
285 remain in remission. This finding raises the question of whether MUO dogs might benefit
286 from receiving a very small dose of prednisolone in the longer-term instead of discontinuing
287 at 34 weeks. However, further studies will be required in order to substantiate this hypothesis.

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334 **TABLES AND FIGURES**

335 **Table 1**

336 Summary of qualitative and quantitative variables at first presentation for the dogs of each

337 protocol group

		CRI group Median (range)	CRI + SC group Median (range)	*P* value
Number of dogs		42	41	
Sex	**Female**	21	22	0.83
	Male	21	19	
Age (months)		45 (8-111)	47 (7-116)	0.69
Time to presentation (days)		3 (0-13)	2 (0-26)	0.41
CSF TNCC (cells/microL)		39 (8-792)	35 (9-693)	0.64
CSF protein concentration (mg/dL)		53 (19-112)	46 (16-98)	0.47

338 CRI: constant rate infusion; CSF: cerebrospinal fluid; TNCC: total nucleated cell count

339

340 **Table 2**

341 Success, relapse and death rates of the dogs of each protocol group at 34 weeks (prednisolone

342 discontinuation), 40 weeks (6 weeks after prednisolone discontinuation), 74 weeks (end of the

343 cytosine arabinoside SC injections for the CRI + SC group) and 36 months follow-up. Dogs

344 that were lost to follow-up (2 dogs for each group: at 301 and 372 days for the CRI group and

345 at 270 and 472 days from the CRI + SC group) were removed at their respective time points

346 when lost to follow-up.

		CRI group Nb of dogs (%)	CRI + SC group Nb of dogs (%)	*P* Value
34 weeks	**Success**	28/42 (66.7)	31/41 (75.6)	0.47

	Relapse	8/42 (19)	6/41 (14.6)	0.77
	Death	6/42 (14.3)	4/41 (9.8)	0.74
40 weeks	**Success**	27/42 (64.3)	26/40 (65)	1
(10 months)	**Relapse**	9/42 (21.4)	10/40 (25)	0.80
	Death	6/42 (14.3)	4/40 (10)	0.74
72 weeks	**Success**	18/40 (45)	17/39 (43.6)	1
(18 months)	**Relapse**	16/40 (40)	18/39 (46.1)	0.65
	Death	6/40 (15)	4/39 (10.3)	0.74
36 months	**Success**	13/40 (32.5)	14/39 (35.9)	0.81
	Relapse	21/40 (52.5)	21/39 (53.8)	1
	Death	6/40 (15)	4/39 (10.3)	0.74

Nb = number

Figure 1

Treatment protocol for dogs with meningoencephalomyelitis of unknown origin treated with a cytosine arabinoside constant rate infusion with (CA CRI + SC protocol) or without (CA CRI protocol) subsequent subcutaneous injections. Both groups received adjunctive prednisolone. A cycle refers to 4 SC injections, 12 hours apart. CA: cytosine arabinoside; CRI: constant rate infusion; q12h: twice daily; q24h: once daily; q48h: every other day; q72h: one in three days.

Figure 2

Kaplan Meier survival curve on long-term (> 36 months) follow-up of dogs diagnosed with meningoencephalomyelitis of unknown origin treated with a combination of

prednisolone and cytosine arabinoside constant rate infusion with (A) or without (B) subsequent subcutaneous injections.