Comparison of oral administration of lomustine and prednisolone or prednisolone alone as treatment for granulomatous meningoencephalomyelitis or necrotizing encephalitis in dogs

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Objective—To compare oral administration of lomustine and prednisolone with oral administration of prednisolone alone as treatment for granulomatous meningoencephalomyelitis (GME) or necrotizing encephalitis (NE) in dogs.

Design—Retrospective cohort study.

Animals—25 dogs with GME and 18 dogs with NE (diagnosis confirmed in 8 and 5 dogs, respectively).

Procedures—Records of dogs with GME or NE were reviewed for results of initial neurologic assessments and clinicopathologic findings, treatment, follow-up clinicopathologic findings (for lomustine-treated dogs), and survival time. Dogs with GME or NE treated with lomustine and prednisolone were assigned to groups 1 (n = 14) and 3 (10), respectively; those treated with prednisolone alone were assigned to groups 2 (11) and 4 (8), respectively.

Results—Prednisolone was administered orally every 12 hours to all dogs. In groups 1 and 3, mean lomustine dosage was 60.3 mg/mt², PO, every 6 weeks. Median survival times in groups 1 through 4 were 457, 329, 323, and 91 days, respectively (no significant difference between groups 1 and 2 or between groups 3 and 4). Within the initial 12 months of treatment, median prednisolone dosage was reduced in all groups; dosage reduction in group 1 was significantly larger than that in group 2 at 6, 9, and 12 months. Combination treatment most frequently caused leukopenia, but had no significant effect on liver enzyme activities.

Conclusions and Clinical Relevance—In dogs with GME and NE, oral administration of lomustine and prednisolone or prednisolone alone had similar efficacy. Inclusion of lomustine in the treatment regimen was generally tolerated well. (J Am Vet Med Assoc 2011;238:337–345)

Granulomatous meningoencephalomyelitis, NME, and NLE belong to a group of idiopathic encephalitides in dogs. The ongoing debate regarding the most appropriate terminology for those diseases reflects the fact that the exact underlying cause and pathogenesis of each have not yet been determined. However, 1 or several different factors are believed to trigger an excessive immunologic response resulting in inflammatory changes in the CNS. Therefore, treatment has been aimed at suppression of immune-mediated inflammatory changes. Traditionally, administration of prednisolone in immunosuppressive doses to dogs with GME has resulted in survival times that range from several days to > 3 years. In later reports of dogs with GME, treatment with prednisolone resulted in median survival times of 41 and 28 days (overall range, 3 to 63 days). Prednisolone treatment of dogs with NME or NE has had similar results. In a group of 7 dogs with NME, mean survival time was 38.3 days but only 1 and 2 days for 2 Yorkshire Terriers. In another group of 6 Yorkshire Terriers with NE, median survival time was 0 days (range, 0 days to 18 months); similarly, in a group of 5 Chihuahuas with NME, median survival time was 0 days (range, 0 days to 6 weeks).

Dogs receiving long-term glucocorticoid treatment usually develop polyuria-polydipsia, polyphagia, and...
panting. More chronic adverse effects of glucocorticoid excess include steroid hepatopathy, alopecia, poor wound healing, urinary tract infections, and muscle weakness. Therefore, other medications have been used alone or in combination with corticosteroids to achieve similar or prolonged survival times with less severe adverse effects; such medications include cycosine arabinoside, procarbazine, cyclosporine, azathioprine, lomustine, mycophenolate motefil, and vincristine with cyclophosphamide and prednisolone.

Alternatively, lomustine has been used sporadically for treatment of GME in dogs, but to our knowledge, there are no published data to date except for research abstracts. It is known that lomustine, a bifunctional alkylating agent in the nitrosurea subclass, is effective in the treatment of lymphoma in dogs. Lomustine is thought to act via induction of intrasand and strand DNA cross-linking by transferring a chloroethyl group from the chloroethyl-nitrosurea to the O methy group of guanine. The low molecular weight and the lipophilic properties of lomustine allow its passage through the blood-brain barrier; thus, this drug has potential use in the treatment of neoplastic intracranial lesions. In addition, results of a study in humans have indicated that lomustine is able to suppress B- and T-cell proliferation, both of which play a major role in the development of inflammatory lesions associated with GME and NE. Because of these actions—effective blood-brain barrier penetration and lymphocyte suppression—lomustine seems to be a potential option to treat intracranial inflammatory diseases. The purpose of the study reported here was to compare oral administration of lomustine and prednisolone with oral administration of prednisolone alone as treatment for GME or NE in dogs.

Materials and Methods

Case selection—For the purposes of the study, NME and NLE were included in the term NE. Dogs with GME and NE that were evaluated in June 2000 through December 2008 were identified retrospectively from the hospital databases of the Department of Small Animal Medicine, University of Leipzig, or the Department of Clinical Veterinary Medicine, Division of Clinical Neurology, University of Bern. Diagnosis of GME or NE was based on results of histologic examination of needle-biopsy brain specimens obtained before initiation of treatment or suspected diagnosis was confirmed at necropsy after treatment; otherwise, it was considered a presumptive diagnosis.

Medical records review—For inclusion in the study, each medical record had to include specific information as follows: results of initial neurologic examination, CBC, serum biochemical analyses, brain MRI, CSF analysis, and survival time. For dogs treated with lomustine and prednisolone, additional information regarding results of a follow-up CBC and assessment of liver enzyme activities and prednisolone dosages for the initial 12 months of treatment had to be available. Results of tests for antibodies against infectious organisms, results of histologic examination of brain biopsy specimens or postmortem brain tissue specimens, and cause of death were retrieved when available. Survival time (defined as the interval between initial evaluation at our hospitals and death or euthanasia) as well as the underlying reason for death or euthanasia was recorded if available. Dogs were included in the study if they survived for at least 1 week after initiating medical treatment; this interval was considered sufficient to allow the medications to take effect.

Diagnosis of GME or NE—Presumptive diagnosis of GME was established in dogs that fulfilled specific criteria as follows: age, 1 to 10 years; breed, small or toy; diffuse or multifocal lesions affecting mainly white matter detected via MRI; and either high nucleated cell count (> 5/μL), high total protein concentration (> 0.25 g/L), or both in a cisternal sample of CSF. Antibodies against *Ehrlichia canis*, *Toxoplasma gondii*, and *Neospora caninum* were not detected in serum and CSF samples, and antibody against canine distemper virus was not detected in CSF samples in 19 of 25 dogs.

Presumptive diagnosis of NE was established in dogs that fulfilled specific criteria as follows: age, 1 to 10 years; breed, small or toy; multifocal lesions detected via MRI, of which ≥ 1 was a cavitation lesion; and high nucleated cell count (> 5/μL) and total protein concentration (> 0.25 g/L) in a cisternal sample of CSF. Analysis of a CSF sample was not considered mandatory in Yorkshire Terriers as long as each patient of this breed met the other criteria because a sufficient amount of CSF for complete analysis could not be obtained in all dogs of this breed.

Some cases of GME or NE were confirmed via histologic examination of needle-biopsy brain specimens obtained prior to initiation of any treatment. For those dogs, the other diagnostic criteria did not have to be met.

Group assignment—Each dog with GME was allocated to 1 of 2 groups on the basis of the treatment it received as follows: treatment with a combination of lomustine and prednisolone, group 1 (n = 14); treatment with prednisolone alone, group 2 (11). Each dog with NE was similarly allocated to 1 of 2 groups on the basis of the treatment it received as follows: treatment with combination of lomustine and prednisolone, group 3 (n = 10); treatment with prednisolone alone, group 4 (8).

Treatment—All dogs with presumptive antemortem diagnosis of GME or NE were initially treated orally with prednisolone (0.17 to 2.5 mg/kg [0.08 to 1.14 mg/lb]) twice daily starting on day 1 immediately after diagnostic testing had been completed. In groups 1 and 3, treatment with lomustine was commenced in addition to prednisolone administration after antibody testing yielded negative results in presumptive cases or after histologic examination of brain biopsy specimens confirmed the diagnosis. The initial dosage of lomustine ranged from 44 to 88 mg/m² (median dosage, 58 mg/m² [95% CI, 51 to 65 mg/m²]; mean dosage, 60.3 mg/m²) administered orally every 6 weeks.

One week after starting lomustine treatment, the dosage of prednisolone was tapered in a stepwise manner to the lowest effective dose. The initial dosage of prednisolone was recorded as the mean daily prednisolone dosage during the first 3 months, months 4 though 6, months 6 to 9, and months 9 and 12 of treatment. Every
Statistical analysis was performed by use of commercial software. Continuous data were tested for normal distribution by use of the Kolmogorov-Smirnov test. Data are reported as mean ± SD or median and 95% CI, depending on the normality of data distribution. In addition, ranges are reported if considered relevant. For comparison of survival times between groups, Kaplan-Meier survival curves and nonparametric log rank tests were used. Group means or medians of numeric variables were compared by use of appropriate parametric and nonparametric t tests and 1-way ANOVAs (depending on the number of comparison groups and distribution). For those variables measured at several time points, the aforementioned analyses were run for each relevant time point. The following comparisons were made: survival time (group 1 vs group 2 and group 3 vs group 4); prednisolone dosage between group 1 and 2 and between group 3 and 4 as well as within group 1 and 3 at day 1, 3 months, 6 months, 9 months, and 12 months); WBC, RBC, and platelets counts (group 1 vs group 3 at day 1 and every 7 to 10 days following every lomustine administration); and serum alanine aminotransferase and alkaline phosphatase serum activities (group 1 vs group 3 at day 1, 3 months, 6 months, 9 months, and 12 months).

Categorical data were evaluated by use of frequency tables, which were tested for difference of homogenous distribution with a χ² test. The null hypothesis was that there was a homogenous distribution or a lack of association between variables. For the comparison of proportions between 2 groups, a 2-sided Fisher exact test was used. The following comparisons of categorical data were made: number of female and male dogs with GME (groups 1 plus 2) versus the number of each sex among dogs with NE (groups 3 plus 4). For all analyses, a value of P ≤ 0.05 was considered significant.

Results

Dogs—Records of 25 dogs with GME and 18 dogs with NE were included in the study. Diagnosis was established on the basis of the results of histologic examination of brain biopsy specimens in 2 dogs with GME and 2 dogs with NE. Presumptive diagnosis was confirmed at necropsy in 6 dogs with GME and in 3 dogs with NE. In addition, results of postmortem examination of brain biopsy specimens confirmed a diagnosis of NE in 2 dogs. Therefore, diagnosis was finally confirmed in 8 of 23 GME-affected dogs and in 3 of 18 NE-affected dogs.

Among the GME-affected dogs, breeds included Pekingese (n = 3), Chihuahua (2), Jack Russell Terrier (2), mixed (2), Shih Tzu (2), West Highland White Terrier (2), Yorkshire Terrier (2), Affenpinscher (1), Bolonka (1), Dachshund (1), French Bulldog (1), Golden Retriever (1), Lhasa Apso (1), Miniature Pinscher (1), Miniature Schnauzer (1), Siberian Husky (1), and Toy Poodle (1). There were 11 females and 14 males (proportion of females to males, 0.79). The mean age of the dogs in groups 1 and 2 at the time of the initial evaluation was 5.6 years (95% CI, 4.4 to 6.8 years) and 5.1 years (95% CI, 3.4 to 6.8 years), respectively.

Among the NE-affected dogs, breeds included Yorkshire Terrier (n = 14), Chihuahua (1), French Bulldog (1), Maltese (1), and Pekingese (1). There were 11 females and 7 males (proportion of females to males, 1.6). The mean age of the dogs in groups 3 and 4 at the time of the initial evaluation was 3.9 years (95% CI, 2.6 to 5.3 years) and 3.9 years (95% CI, 1.6 to 6.1 years), respectively.

The proportion of females to males among the GME- and NE-affected dogs did not differ significantly. Dogs with GME were significantly (P = 0.039) older than the dogs with NE. Compared with male dogs in either group, female dogs with GME or NE were affected at a significantly (P < 0.001) younger age.

Prednisolone dosage administered to dogs with GME—Over time, the median total amount of prednisolone administered each day to dogs in group 1 was reduced; within the first 12 months of treatment, the dosage of prednisolone was decreased from 2.1 to 0.2 mg/kg/d (0.95 to 0.09 mg/lb/d), compared with a dosage reduction from 1.4 to 0.6 mg/kg/d (0.64 to 0.27 mg/lb/d) in dogs treated with prednisolone alone. Compared with
the initial prednisolone dosage in group 1, the dosage was significantly different at 3 months \((P < 0.001)\); similarly, the difference in dosages at 3 and 6 months was significant \((P = 0.001; \text{Figure 1})\). Comparison of the prednisolone dosage administered to dogs in groups 1 and 2 over time revealed that dogs treated with lomustine and prednisolone (group 1) received significantly lower dosages of prednisolone at 6 months \((P = 0.003)\), 9 months \((P = 0.002)\), and 12 months \((P = 0.013)\).

Information in the medical records indicated that administration of prednisolone was discontinued for 4 of the 14 dogs that also received lomustine. One of those dogs was treated for 3 months with lomustine and prednisolone, after which prednisolone administration was discontinued; 1 month later, the owner decided to discontinue administration of lomustine. The dog had no clinical signs of GME for 10 months before it was euthanatized because of renal failure. Diagnosis of GME was confirmed at necropsy. Another of the 4 dogs was treated with lomustine and a tapering dosage of prednisolone for 6 months, at which time prednisolone administration was discontinued. Three months later, administration of a low dosage of prednisolone was commenced for a 3-month period, but then treatment was discontinued after brain MRI and CSF analysis revealed no abnormalities. The dog had seizures every 3 to 4 months for 26 months thereafter; at that time, the dog was euthanatized because of renal failure.

Necropsy confirmed the presumed diagnosis of GME. A third dog was treated with lomustine and prednisolone for 6 months before prednisolone administration was discontinued. The dog received only lomustine for at least 6 months. Diagnosis of GME in this dog was established on the basis of histologic examination of a brain biopsy specimen prior to treatment. The remaining dog was treated with lomustine and a tapering dosage of prednisolone for 22 months; at that time, treatments with lomustine and prednisolone were both discontinued because brain MRI and CSF analysis revealed no abnormalities. At 9 months without treatment, the dog was considered neurologically normal. Prednisolone administration was not discontinued for any of the dogs in group 2.

**Prednisolone dosage administered to dogs with NE—**

Over time, the median total amount of prednisolone administered each day to dogs in group 3 was reduced; within the first 12 months of treatment, the dosage of prednisolone was decreased from 1.9 to 0 mg/kg/d \((0.86 \text{ to } 0 \text{ mg/lb/d})\) and 2.1 to 1 mg/kg/d \((0.95 \text{ to } 0.45 \text{ mg/lb/d})\). Compared with the initial prednisolone dosage, the dosage was significantly \((P = 0.002)\) different at 3 months; similarly, the difference in dosages at 3 and 9 months was significant \((P = 0.020; \text{Figure 2})\). Comparison of the prednisolone dosage administered to dogs in groups 3 and 4 over time revealed no significant difference at any time point. However, the prednisolone dosage reduction in group 1 was significantly larger than that in group 3 at 6 months \((P = 0.003)\), 9 months \((P = 0.002)\), and 12 months \((P = 0.013)\).

Information in the medical records indicated that administration of prednisolone was discontinued for 4 of the
10 dogs that also received lomustine. In those dogs, treatment with prednisolone was discontinued at 3 months (n = 2), 6 months (1), and 9 months (1). After administration of prednisolone was discontinued, 2 of the 4 dogs received lomustine alone for an additional 14 and 18 months. Diagnosis of NE was confirmed histologically in both of those dogs (on the basis of results of examination of a biopsy specimen for 1 dog and at necropsy for the other). One of those dogs was euthanatized because of hemorrhagic gastroenteritis, and the other was euthanatized because of a cluster of seizures with subsequent neurologic deterioration. The other 2 dogs with suspected NE received lomustine alone for at least 4 and 5.5 months, respectively, without developing noticeable neurologic signs. Prednisolone administration was not discontinued for any of the dogs in group 4.

**Survival time for dogs with GME**—Median survival times in groups 1 and 2 were 457 days (95% CI, 107 to 709 days) and 323 days (95% CI, 39 to 542 days), respectively (Figure 3). Survival time did not differ significantly (P = 0.34) between groups. One of the 14 dogs in group 1 was still alive after 11.9 months of treatment, as were 3 of the 11 dogs in group 2 after 12.2, 21.1, and 33.2 months of treatment, respectively. Comparison of survival time in groups 1 and 2 adjusted for influences of age and sex revealed a significant (P = 0.026) influence of age at initial evaluation on survival time.

Separate statistical evaluation of cases with only histologic confirmation of diagnosis failed because of low numbers of dogs. However, dogs with histologically confirmed GME that were treated with lomustine and prednisolone (n = 8) had a median survival time of 14.5 months (range, 0.4 to 38.6 months).

**Cause of death or reason for euthanasia for dogs with GME**—The cause of death or reason for euthanatization was documented for 9 of 13 dead dogs in group 1; 3 died or were euthanatized because of recurrence of neurologic signs, and 6 died or were euthanatized because of non-neurologic conditions such as renal failure, cardiac failure, hemorrhagic gastroenteritis, septic shock, and suspected liver failure. The reason for euthanasia was documented for 5 of 8 dead dogs in group 2; 1 was euthanatized because of chronic renal failure, and 4 were euthanatized because of a lack of improvement or relapse of neurologic signs.

**Survival time for dogs with NE**—The median survival times in groups 3 and 4 were 329 days (95% CI, 98 to 628 days) and 91 days (95% CI, 7 to 494 days), respectively (Figure 4). Survival time did not differ significantly (P = 0.28) between groups. Two of the 10 dogs in group 3 were still alive after 11.8 and 13.0 months of treatment, whereas all dogs in group 4 were not.

Separate statistical evaluation of cases with only histologic confirmation of diagnosis failed because of low numbers of dogs. However, dogs with histologically confirmed NE that were treated with lomustine and prednisolone (n = 5) had a median survival time of 329 days (range, 99 to 629 days).

**Cause of death or reason for euthanasia for dogs with NE**—The cause of death or reason for euthanasia was documented for all 8 dead dogs in group 3; 3 died or...
were euthanatized because of recurrence of neurologic signs, and 5 died or were euthanatized because of other medical conditions such as pleural effusion, cardiac failure, septic shock, and gastrointestinal hemorrhage. The reason for euthanasia was documented for 5 of the 8 dogs in group 4, all of which were euthanatized because of a lack of improvement or relapse of neurologic signs.

CBC and liver enzyme activity data—Clinicopathologic data relating to dogs with GME and NE that received both lomustine and prednisolone (groups 1 and 3; n = 24) were evaluated together. Sufficient data for statistical analysis were available for 64 weeks of treatment; 80 WBC counts, 61 RBC counts, 65 platelet counts, 45 alanine aminotransferase activities, and 40 alkaline phosphatase activities were reported. In the dogs treated with lomustine and prednisolone, there was no significant overall change in mean ± SD WBC count, RBC count, or platelet count, although RBC count decreased significantly (P = 0.011) from 7.0 X 10¹² cells/L ± 0.84 X 10¹² cells/L to 6.1 X 10¹² cells/L ± 0.84 X 10¹² cells/L after the first administration of lomustine. However, the WBC count was low (reference range, 6 X 10⁹ cells/L to 12 X 10⁹ cells/L) in 25 of the 80 reported measurements; 2 measurements were < 2 X 10⁸ cells/L, 9 measurements were 2 X 10⁸ cells/L to < 3 X 10⁹ cells/L, and 14 measurements were 3 X 10⁹ cells/L to 5 X 10⁹ cells/L. One dog developed a severe leukopenia after the third administration of lomustine (WBC count, 1 X 10⁹ cells/L) and died shortly thereafter as a result of septic shock.

The mean RBC count was 3 X 10¹² cells/L to 5 X 10¹² cells/L in 4 of 61 measurements (reference range, 6 X 10¹² cells/L to 9 X 10¹² cells/L). The mean platelet count was low (reference range, 150 X 10⁹ platelets/L to 500 X 10⁹ platelets/L in 3/65 measurements); 2 measurements were < 30 X 10⁹ platelets/L, and 3 measurements were 30 X 10⁹ platelets/L to 100 X 10⁹ platelets/L.

Serum activities of alanine aminotransferase and alkaline phosphatase did not change significantly in the dogs administered lomustine and prednisolone during the course of treatment (Figure 5). In general, mean values increased during the initial 9 months of treatment and subsequently decreased at 12 and 15 months, but the changes were not significant.

Discussion

Analysis of data in the present study revealed that treatment with a combination of lomustine and a tapering dosage of prednisolone resulted in median survival times of 457 days in GME-affected dogs and 329 days in NE-affected dogs. The initial 3 to 4 months of treatment appeared to be a critical period, and dogs that survived that period were likely to survive for at least 9 months. This finding may reflect the dogs’ response to and tolerance of the medications. Dogs in which response to treatments was poor or adverse drug effects developed were usually euthanatized or died within the first few months after starting treatments, whereas dogs in which an initial positive response was evident had a better long-term prognosis. A similar pattern was identified in a recent prospective study in which 2 treatment protocols in dogs with MUO were compared.

Median survival times for dogs that received lomustine in addition to prednisolone were longer than the median survival times for dogs that received prednisolone alone, but those differences were not significant. To our knowledge, the only report of a comparable protocol is a research abstract that describes 8 dogs with presumed noninfectious encephalitis, which received treatment with lomustine and prednisolone; the treatment regimen resulted in similar findings, with clinical improvement in 7 dogs and survival times of 210 to 740 days.

Survival times of the dogs that received lomustine in the present study were compared with survival times...
reported for dogs that were treated with other medications alone or in combination with prednisolone (Appendix). It is, however, virtually impossible to directly compare any of those study results with each other or with the findings of the present study. The reported studies often included dogs with different diseases; dogs had GME or NE, or MUO. In some studies, in which dogs with a specific disease were investigated, histologic confirmation of the disease was lacking; therefore, the dogs were given a presumptive diagnosis only. The same holds partially true for the study of this report, in which 8 of 25 dogs with GME and 5 of 18 dogs with NE had a histologically confirmed diagnosis. We cannot definitely exclude the possibility that some cases of NE were misdiagnosed as GME, although the opposite seems to be less likely because of the presence of cavitating lesions. However, survival times for dogs for which the diagnosis was histologically confirmed were similar to the survival times for all dogs (ie, those with a presumptive or confirmed diagnosis together). This underscores the need for prospective studies to include patients with histologically confirmed disease, ideally confirmed on the basis of histologic examination of brain biopsy specimens obtained prior to initiating treatment.

One of the objectives of the present study was to investigate the possible reduction of the prednisolone dosage if it was combined with lomustine administration. The data indicated that prednisolone dosage could be significantly reduced in dogs with GME as well as in dogs with NE without interfering with control of encephalitis. With regard to dogs with GME, the initial median prednisolone dosage of 2.1 mg/kg/d was reduced to 0.2 mg/kg/d after 12 months of treatment. Similar results were achieved in dogs with NE, for which the median initial dosage of 1.9 mg/kg/d was tapered to 0 mg/kg/d at 12 months of treatment. Most of the dosage reduction was achieved within the first 3 to 6 months of treatment. However, compared with dogs treated with prednisolone alone, a prednisolone-sparing effect of lomustine was evident in GME-affected dogs only. The NE-affected dogs treated with lomustine and prednisolone required a much lower dosage of prednisolone, compared with findings in dogs receiving prednisolone alone; however, that difference was not significant, which was most likely because the variation in the individual dosages was large.

It is noteworthy that prednisolone administration could be discontinued in 4 dogs with GME and 4 dogs with NE. In 3 of those GME-affected dogs, lomustine administration was discontinued also, which suggests that lomustine or its combination with prednisolone may be able to suppress the inflammatory response for a longer period.

Data regarding prednisolone dosage reduction in dogs with GME or NE for comparison with the findings of the present study are limited. In 1 study to evaluate combination treatment with procarbazine and prednisolone in dogs with GME, the prednisolone dosage was reduced or administration discontinued in 17 of 21 dogs. In a case series report, complete substitution of prednisolone with cyclosporine was achieved in 3 dogs with suspected GME; the follow-up period for those dogs ranged from 7 to 9 months. In another case series, the combination of cyclosporine and prednisolone in 4 dogs with histologically confirmed NE resulted in reduction of the prednisolone dosage from 2 to 1 mg/kg/d (0.91 to 0.45 mg/lb/d) within 4 weeks after initiating treatment. That reported dosage reduction was achieved more rapidly than was the dosage reduction in the present study. The data in the present study suggested that the rate of dosage reduction could have been increased because only 1 dog had recurrence of neurologic signs after a dosage reduction.

Another objective of the present study was to evaluate adverse effects of the lomustine-prednisolone treatment on CBC variables and serum liver enzyme activities. There was no significant decrease in the CBC variables during the first 64 weeks of treatment, with the exception of the RBC count, which decreased significantly after the first dose of lomustine but subsequently returned to the pretreatment value at the 14-week time point.

Serum activities of alanine aminotransferase and alkaline phosphatase did not change significantly over the treatment period of 64 weeks, but appeared to increase up to 9 months after starting treatment. The subsequent decrease in liver enzyme activities after 9 months could be related to the decreasing prednisolone dosage, which would imply that administration of prednisolone, alone or in combination with lomustine, is the major factor causing increases in liver enzyme activities.

The most common dose-limiting toxic effect of lomustine is leukopenia, which typically develops 7 days after administration in up to 21.7% of dogs. Anemia and thrombocytopenia develop less commonly. Thrombocytopenia seems to be a cumulative effect, whereas leukopenia may be detected after the first dose. In the study of this report, severe leukopenia (< 3 X 10^9 cells/L) developed in 4 dogs after the first administration of lomustine, whereas severe thrombocytopenia was detected after 6 months of treatment. Dogs that developed severe leukopenia after the first administration of lomustine were often leukopenic after the following doses as well, which may reflect an individual hypersensitivity to lomustine. Therefore, dosage adjustment should be performed even after the first administration of the drug, especially when leukopenia develops.

Other common adverse effects of lomustine include liver toxicosis in up to 86% of treated dogs and gastrointestinal toxicosis in up to 22%. Those results are based on much more aggressive treatment protocols than those used in the dogs of this report. With the more conservative protocol in the present study, slight elevation of serum liver enzyme activities was detected, but obvious signs of liver failure were evident after 23.5 months of lomustine treatment in only 1 dog.

To date, there are no reliable data on the adverse effects of lomustine in dogs treated for > 18 months. Dogs in the present study were treated with lomustine for as long as 23.5 months. Two dogs that received lomustine for 21 months died as a result of hemorrhagic gastroenteritis; 1 of them also had pleural effusion. Results of complete necropsy were not available for those dogs, so
it is not known whether the clinical signs were related to lomustine treatment or to other diseases. Two other dogs that had received lomustine for 4 and 9 months died of renal failure after lomustine administration was discontinued for 10 and 26 months, respectively. To the authors' knowledge, renal failure has not been reported as a complication of lomustine treatment. However, a causative relationship between those 2 cases of renal failure and previous lomustine treatment cannot be excluded completely.

In general, in 11 of 17 dogs treated with lomustine and prednisolone, the clinical signs resulting in death or euthanasia were not neurologic, which can be interpreted as an indication of the efficacy of lomustine treatment or the potential risk associated with long-term lomustine treatment. Extending the dosing interval in dogs that are well controlled with lomustine alone may be a potential way to reduce adverse effects of long-term administration.

The data obtained in the present study indicated that the efficacy of lomustine administered orally at a dosage of approximately 60 mg/m² every 6 weeks in combination with prednisolone was similar to that of prednisolone alone in dogs with GME and NE. It appears that the dosage of prednisolone can be tapered during the course of treatment in those dogs; however, comparison of the 2 treatment protocols (lomustine and prednisolone vs prednisolone alone) revealed that prednisolone dosages were lower only in dogs with GME that received the combination treatment. Nevertheless, for some dogs with GME or NE, administration of prednisolone can be discontinued completely. With the exception of inflammatory or malacic lesions in 3 dogs (abstr), in Proceedings. 2007. 230:1866–1869.


References

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f. NCSS 2007, NCSS, Kaysville, Utah.


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**Appendix**

Reported survival times of dogs with GME, NLE, NME, or MUO that received treatments in addition to administration of prednisolone.

<table>
<thead>
<tr>
<th>Disease (No. of dogs)</th>
<th>No. of dogs with histologic confirmation of diagnosis</th>
<th>Treatment</th>
<th>Survival time</th>
<th>Reference or footnote</th>
</tr>
</thead>
<tbody>
<tr>
<td>GME (3)</td>
<td>0</td>
<td>Azathioprine + prednisolone</td>
<td>3 mo</td>
<td>8</td>
</tr>
<tr>
<td>MUO (3)</td>
<td>0</td>
<td>Leflunomide + prednisolone</td>
<td>&gt; 12 mo</td>
<td>b</td>
</tr>
<tr>
<td>NLE or NME (1), MUO (9)</td>
<td>1</td>
<td>Cytosine arabinoside + prednisolone</td>
<td>Median, 531 d</td>
<td>25</td>
</tr>
<tr>
<td>MUO (10)</td>
<td>3</td>
<td>Ciclosporine + ketoconazole or ciclosporine + prednisolone</td>
<td>Median, 830 d</td>
<td>9</td>
</tr>
<tr>
<td>GME (21)</td>
<td>0</td>
<td>Procarbazine + prednisolone</td>
<td>Median, 14 mo</td>
<td>11</td>
</tr>
<tr>
<td>NLE or NME (7)</td>
<td>7</td>
<td>Ciclosporine + prednisolone vs prednisolone alone (n = 3)</td>
<td>Mean, 306 ± 95 d vs 58 ± 30 d</td>
<td>3</td>
</tr>
<tr>
<td>GME (5)</td>
<td>0</td>
<td>Mycophenolate mofetil</td>
<td>Up to 8 mo</td>
<td>c</td>
</tr>
<tr>
<td>MUO (11)</td>
<td>0</td>
<td>Cytosine arabinoside + prednisolone</td>
<td>From 78 to &gt; 603 d</td>
<td>12</td>
</tr>
<tr>
<td>MUO (19)</td>
<td>0</td>
<td>Vincristine + cyclophosphamide + prednisolone (n = 10) vs cytosine arabinoside + prednisolone (9)</td>
<td>12 months’ survival, 4 vs 5 dogs</td>
<td>13</td>
</tr>
<tr>
<td>MUO (40)</td>
<td>0</td>
<td>Azathioprine + prednisolone</td>
<td>Median, 1,834 d</td>
<td>14</td>
</tr>
</tbody>
</table>