The efficacy and toxicity of Dexamethasone, Melphalan, Actinomycin D, Cytosine Arabinoside (DMAC) as a rescue protocol for dogs with multicentric lymphoma.

F Oshima[1], T Kobayashi[1], E Fukazawa[1], Y Nakano[1], T Yamagami[2], Y Shiraishi[2]
[1] Japan Small Animal Cancer Center, [2]Japan Small Animal Medical Center

Introduction

The dexamethasone, melphalan, actinomycin D, cytosine arabinoside protocol (DMAC) was reported as a well-tolerated treatment for relapsed canine lymphoma. However, when the DMAC was used in Japan, we often encountered severe hematological and gastrointestinal toxicity.

The purpose of this study is to evaluate the efficacy and toxicity of the DMAC as a rescue protocol in dogs with multicentric lymphoma.

Methods

The medical records of 16 dogs with relapsed multicentric lymphoma treated with the DMAC protocol at Japan Small Animal Cancer Center from October 2007 to April 2011 were reviewed. All dogs were resistant to UW-25 protocol. The diagnosis was confirmed by histopathology or cytology. The type of immunophenotype was determined with Immunohistochemistry using CD3 and CD79a or clonality assay.

The original DMAC protocol is shown on Table 1. CBC and physical examination findings were available on day-1 and day-8. Serum biochemical panels were performed at the beginning of each cycle. Hematological and gastrointestinal toxicity was evaluated according to the VCOG-CTCAE version 1.0 criteria[1]. Sepsis was defined as systemic inflammatory response syndrome (SIRS) caused by probable infection.

When neutropenia (<2,500/μL), thrombocytopenia (<100,000/μL) or gastrointestinal toxicity higher than grade 2 were seen on day 8, melphalan administration was postponed for 4-7 days. When neutropenia (<1,500/μL), thrombocytopenia (<75,000/μL) and/or sepsis were seen during the first cycle, 25% dose reductions for both actinomycin D and cytosine arabinoside were made for subsequent DMAC protocol. Response was classified according to the World Health Organization (WHO) criteria.

Table 1. The original DMAC protocol

Drug	Route	Day1	Day8
Actinomycin D 0.75mg/m^2	IV for 10min	○	-
Cytosinearabinoside 300mg/ m^2	SC or IV over 4hs	○	-
Dexamethasone 1.0mg/kg	IV	○	○
*Melphalan 20mg/ m^2	PO	-	○

Results

The median age of 16 dogs was 5 yeas (3-10 years). Eleven dogs were male (5 castrated) and 5 were female (3 spayed). Median body weight was 14.1kg (4.5-39.2 kg). They were all pure breeds including Golden Retriever (n= 4), Welsh corgi (3), Shi Tzu (2) and 7 other breeds (1 each). Ten of 16 (62.5%) had lymphoma of B-cell origin and the other 6 (37.5%) had T-cell lymphoma. Four dogs received more than one rescue protocol prior to the DMAC including CCNU + L-asparaginase (n= 2), CCNU + dacarbazine(1), doxorubicin + dacarbazine (1) and chlorambucil (1).

One dog died due to tumor progression 2 days after initiation of the DMAC and 15 dogs were evaluated for adverse events. Grade 1 or higher neutropenia, thrombocytopenia, vomiting and diarrhea were observed in 10/15 (66.6%), 12/15 (80.0%), 4/15 (26.6%) and 8/15 (53.3%) dogs, respectively (Table 2). Sepsis was seen in 6/15 (40.0%) at a median of 9 days (3-12 days) after initiation of the DMAC. All septic dogs had grade1 (n=1), grade3 (2) and grade4 (3) neutropenia with median neutrophil counts of 406/μl. No dog died due to the sepsis. Treatment delay on day-8 was necessary due to adverse events in 6/11 (54%) including 4 dogs with neutropenia (median neutrophil counts = 2,520/μl) and/or thrombocytopenia (median platelet counts = 84,000/μl), 1 dog with grade 2 gastrointestinal toxicity and 1 dog with grade 1 neutropenia with fever (39.5℃). Day 8 chemotherapy was not administered due to tumor progression (n= 4), grade 4 neutropenia (1) and grad 3 diarrhea (1). Only 3 dogs could continue the DMAC more than 2 cycles. Two of 3 dogs were required dose reductions due to hematologic and gastrointestinal toxicity.

Overall response rate was 43.7% (CR=31.2%, PR=12.5%) and median response duration was 21days (14-801 days)(Figure 1).

Table 2. Summary of hematological and gastrointestinal toxicity evaluated by VCOG-CTCAE

Grade	1	2	3	4
Neutropenia	4	0	1	5
Thrombocytopenia	5	3	1	3
Vomiting	1	2	1	0
Diarrhea	4	2	2	0

Table 3. Modified DMAC protocol

Drug	Route	Day1	Day8	Day15
Actinomycin D 0.56mg/m^2	IV for 10min	○	-	-
Cytosinearabinoside 225mg/ m^2	SC or IV for 4hs	○	-	-
Dexamethasone 1.0mg/kg	IV	○	-	○
*Melphalan 20mg/ m^2	PO	-	-	○
Blood test	-	CBC,Chem	CBC	CBC

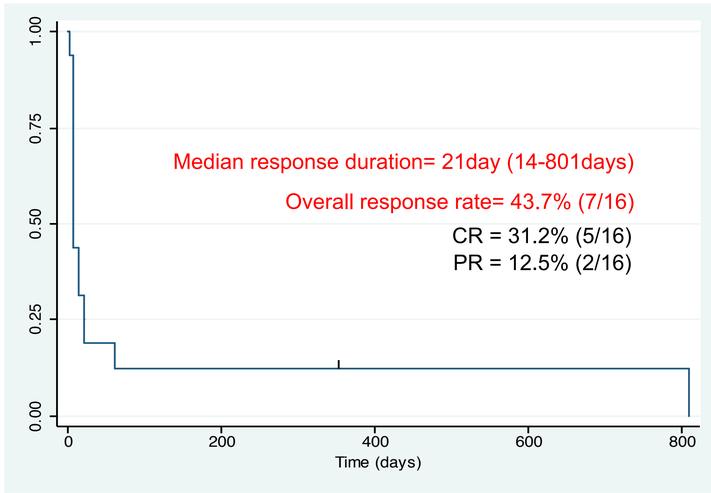

Fig.1 Kaplan-Meier curve for overall response duration in 16 dogs

Discussion

In the original study, grade 1 or higher neutropenia, thrombocytopenia, vomiting and diarrhea were observed in 7/41(17%), 23/41(56%), 9/41(22%) and 0%, respectively. All adverse events in our study were higher than previously reported. The reasons for the differences are unclear, but may be related to the differences in body weight between two countries; median body weight in the original study was 26.5kg vs. 14.1kg in our study. The calculation by the body surface area translation showed that a relative dose for small dogs would be higher than that for larger dogs. In addition, the original study did not perform day 8 CBC routinely and the hematologic toxicity could have been underestimated.

In more than the half of the cases, we are not able to administer day 8 chemotherapy as scheduled. Forty percent of dogs also had sepsis at the median of 9 days. The results indicated that the dose intensity of the original DMAC for relatively small dogs may be too high and dose modification might be required. We are currently using a modified-DMAC protocol for relatively small dogs as shown on Table 3.

The response rate of the original study was 72% and higher than that of our study. The original study suggested that previous treatment with doxorubicin was a negative prognostic factor on the response rate for DMAC. All dogs in our study were treated with and resistant to doxorubicin and this might be negatively affected and possibly associated with relatively lower response rate in our study.

Conclusion

Although the response rate of the DMAC is comparable to other rescue protocols, adverse events were too high and unacceptable for our population. Modification of the dose intensity of the original DMAC might be necessary for relatively small dogs.

Current Contact Address

Fukiko Oshima, DVM. E-mail: julia_aby@me.com

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