pISSN 1598-298X / eISSN 2384-0749
*J Vet Clin* 36(1) : 30-37 (2019)
http://dx.doi.org/10.17555/jvc.2019.02.36.1.30

Journal of Veterinary Clinics
www.ksvc.or.kr

# A Study of Gastrointestinal and Bone Marrow Adverse Events after Administration of Various Chemotherapeutic Agents in Canine Malignant Tumor Patients

**Na-Ni Ji, Joong-Hyun Song, Tae-Sung Hwang, Hee-Chun Lee, Do-HyeonYu and Dong-In Jung[1]**

*Institute of Animal Medicine, College of Veterinary Medicine, Gyeongsang National University, Jinju 52828, South Korea*

(Received: March 20, 2018 / Accepted: January 25, 2019)

**Abstract :** The purpose of this present study was to objectively evaluate gastrointestinal and bone marrow AEs after administration of various chemotherapeutic agents in canines with malignant tumors, using the Veterinary Cooperative Oncology Group-Common Terminology Criteria for Adverse Events (VCOG-CTCAE), which includes descriptive terminology used for adverse events (AEs) reported in dogs and cats. The medical records of 42 dogs with malignant tumor that underwent chemotherapy were reviewed retrospectively. There were no significant differences in the prevalence of gastrointestinal AEs among the 5 chemotherapeutic agents (vincristine, cyclophosphamide, doxorubicin, lomistine, and carboplatin). The prevalence of bone marrow AEs was significantly higher after administration of lomustine than after administration of vincristine or doxorubicin. Grade 1 AEs of the gastrointestinal tract and bone marrow were most often observed after administration of various chemotherapeutic agents. Delayed and cumulative myelosuppression of lomustine in some dogs receiving regular blood examination were identified. The findings of this study will help predict possible gastrointestinal and bone marrow AEs due to the use of chemotherapeutic agents to treat canines with malignant tumors.

***Key words*** **:** adverse events, bone marrow suppression, canine, chemotherapeutic agents, toxicity.

## Introduction

Chemotherapy uses a pharmaceutical agent to kill tumor cells by preventing cell growth and division. Chemotherapy can be administered alone or in combination with surgery, radiation, immunotherapy, and/or molecular targeted therapy (2). The use of chemotherapeutic agents in veterinary medicine depends on the tumor type, stage of the disease, histologic grade of the tumor, and the owner's financial situation (13). Chemotherapeutic agents affect various steps of DNA replication (S phase) and subsequent cell division (M phase). Other chemotherapeutic agents interfere with the signaling processes that trigger entry into the cell cycle and continued cellular proliferation. Anticancer drugs that affect DNA synthesis include alkylating agents, topoisomerase inhibitors, cross-linking agents, and antimetabolites. Antimicrotubule agents inhibit the M phase of the cell cycle. Tyrosine kinase inhibitors inhibit tyrosine kinase, the enzyme that activates signal transduction cascades. The cells affected by chemotherapeutic agents undergo apoptosis or other cell death processes (3).

Most chemotherapeutic agents target rapidly dividing cells, and cannot differentiate between tumor cells and normal cells with a high growth rate. Therefore, chemotherapy agents can also affect rapidly dividing normal cells of the bone marrow, gastrointestinal tract, and hair follicles. Thus, the most common adverse events (AEs) of chemotherapy are myelosuppression, gastrointestinal toxicity (vomiting, diarrhea, anorexia), and alopecia (13,14).

Chemotherapy-related AEs are categorized depending on when the toxicity occurs. Immediately evident toxicities occur within 24 to 48 hours after treatment; acute delayed effects occur 2 to 14 days after treatment; and cumulative/chronic toxicities occur weeks, months, or years after treatment (13). Immediate toxicities include hypersensitivities due to histamine release and acute vomiting induced by acute infusion of antitumor agents (6). Examples of delayed acute effects of chemotherapy include gastrointestinal toxicities and bone marrow suppression (21). Cumulative/chronic toxicities include the hepatotoxicity due to lomustine, cardiac abnormalities due to doxorubicin, and renal disease due to cisplatin and doxorubicin (1,11,16,17). The veterinary cooperative oncology group has published a consensus document of common terminology criteria for adverse events (VCOG-CTCAE), which includes descriptive terminology used for AEs reported in dogs and cats. AEs are divided into 5 grades of severity, as follows: 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 (ADL)), grade 3 (severe or medically significant but not immediately life-threatening; hospitalization indicated; disabling; significantly limiting ADL), grade 4 (life-threatening consequences; urgent intervention indicated), and grade 5 (death related to the AE)

[1]Corresponding author.
E-mail : jungdi@gnu.ac.kr

(22). This system allows more objective evaluation of AEs due to chemotherapy.

Appropriate and effective chemotherapy for specific tumors improves the quality of life (QOL) and the survival time of veterinary cancer patients (13,14,21). However, serious chemotherapy-related AEs decrease the QOL, delay treatment effects, and may be life-threatening to veterinary cancer patients. Therefore, veterinarians treating tumor patients should predict the AEs of each chemotherapy agent, and administer the appropriate preventative and therapeutic treatments to treat the cancer effectively (21).

The purpose of this retrospective study was to objectively evaluate gastrointestinal and bone marrow AEs after administration of various chemotherapeutic agents in canines with malignant tumors using the VCOG-CTCAE.

## Materials and Methods

### Animals

This retrospective study was performed to assess chemotherapy-related AEs in dogs at Gyeongsang National University Animal Medical Center; it included 42 dogs of different breeds, sexes, and ages. All 42 dogs were diagnosed with malignant neoplasia based on imaging evaluation, cytological examination, and histologic examination. Twenty-eight dogs were diagnosed with lymphoma; 26 with multicentric lymphoma, 1 with alimentary lymphoma, and 1 with cutaneous lymphoma. Four dogs were diagnosed with transitional cell carcinoma (TCC), 2 with hemangiosarcoma, 2 with hepatocellular carcinoma (HCC), 2 with meningioma, 1 with gastric adenocarcinoma, 1 with colon adenocarcinoma, 1 with rectal adenocarcinoma, and 1 with choroid plexus papilloma. All dogs received chemotherapy appropriate to the tumor type, stage of the disease, histologic grade of the tumor, and client's financial situation.

### Chemotherapeutic agents

The chemotherapeutic agents used included vincristine (VCR), cyclophosphamide (CP), doxorubicin (DOX), lomustine, and carboplatin, according to the type of tumor and the treatment protocol. VCR, CP, and DOX were used to treat lymphoma per the University of Wisconsin (UW)-Madison L-VCA short protocol (UW-25). DOX was also used to treat dogs with hemangiosarcoma. Lomustine was used to treat lymphoma, HCC, and brain tumor (meningioma and choroid plexus papilloma). Carboplatin was used to treat TCC, HCC, gastric adenocarcinoma, colon adenocarcinoma, and rectal adenocarcinoma.

The chemotherapeutic agents were administered based on body surface area (mg/m$^2$). The median dosage administered of VCR (Vincran®, Reyon Pharmaceutical Co., Ltd., Seoul, South Korea), CP (Endoxan®, Bukwang Pharmaceutical Co., Ltd., Seoul, South Korea), DOX (Doxorubin®, Teva Handok Pharmaceutical, Co., Ltd., Seoul, South Korea), and carboplatin (Carbotinol®, Korea United Pharma Inc., Seoul, South Korea) were 0.5 mg/m$^2$ (range, 0.5-0.7 mg/m$^2$), 239.7 mg/m$^2$ (range, 200-250 mg/m$^2$), 29.3 mg/m$^2$ (range, 20-30 mg/m$^2$), and 273.4 mg/m$^2$ (range, 200-300 mg/m$^2$). All were adminis-

**Table 1.** Grading system for gastrointestinal adverse events based on the VCOG-CTCAE

| Gastrointestinal | | | | | |
|---|---|---|---|---|---|
| Adverse event | Grade | | | | |
| | 1 | 2 | 3 | 4 | 5 |
| Anorexia | Coaxing or dietary change required to maintain appetite | Oral intake altered (< 3 days) without significant weight loss; oral nutritional supplements/appetite stimulants may be indicated | Of > 3 days duration; associated with significant weight loss (> 10%) or malnutrition; IV fluids, tube feeding or force feeding indicated | Life-threatening consequences; TPN indicated; > 5 days duration | Death |
| Definition : A disorder characterized by a loss of appetite | | | | | |
| Diarrhea | Increase of up to 2 stools per day over baseline; no increase in frequency, however, consistency decreased over baseline | Increase of 3-6 stools per day over baseline; medications indicated; parenteral fluids indicated < 48 h; not interfering with ADL | Increase of > 6 stools per day over baseline; incontinence > 48 h; IV fluids > 48 h; hospitalization; interfering with ADL | Life-threatening (e.g. hemodynamic collapse) | Death |
| Definition : A disorder characterized by frequent and watery bowel movements | | | | | |
| Vomiting | < 3 episode in 24 h, medical intervention not indicated | 3-10 episodes in 24 h; 5 < episodes/ day for < 48 h; parenteral fluids indicated < 48 h; medications indicated | Multiple episode > 48 h and IV fluids or PPN/TPN indicated > 48 h | Life-threatening (e.g. hemodynamic collapse) | Death |
| Definition : A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth | | | | | |

IV; intravenously, TPN; total parenteral nutrition, PPN; peripheral parenteral nutrition, ADL; activities of daily living.

**Table 2.** Grading system for bone marrow adverse events of dog based on the VCOG-CTCAE

| Adverse event | Bone marrow | | | | |
|---|---|---|---|---|---|
| | Grade | | | | |
| | 1 | 2 | 3 | 4 | 5 |
| Pack cell volume | 30% to < LLN | 20 to < 30% | 15 to < 20% | < 15% | Death |
| Neutropenia | 1,500 / μL to < LLN | 1,000-1,499 / μL | 500-999 / μL | < 500 / μL | Death |
| Thrombocytopenia | 100,000 / μL to < LLN | 50,000-99,000 / μL | 25,000-49,000 / μL | < 25,000 / μL | Death |

LLN; lower limit of normal.

tered intravenously. Lomustine (CeeNU®, Bristol-Myers Squibb Canada, Montreal, Canada) was administered orally; the median dosage was 62 mg/m$^2$ (range, 60-80 mg/m$^2$).

The total number of VCR doses was 1 (n = 28), 2 (n = 18), 3 (n = 14), 4-6 (n = 13) and 7-8 (n = 10). The total number of CP doses was 1 (n = 23), 2-3 (n = 13) and 4 (n = 11). The total number of DOX doses was 1 (n = 20), 2 (n = 14), 3 (n = 13) and 4 (n = 11). The total number of lomustine doses was 1 (n = 14), 2 (n = 12), 3 (n = 9), 4 (n = 6), 5-6 (n = 5), 7 (n = 3) and 8 (n = 2). The total number of carboplatin doses was 1 (n = 9), 2 (n = 5) and 3 (n = 3).

### Evaluation of chemotherapy-related gastrointestinal and bone marrow adverse events

The medical records of canine patients treated for malignant tumors between November 2008 and September 2017 at the Gyeongsang National University Animal Medical Center were reviewed retrospectively. Gastrointestinal AEs included vomiting, diarrhea, and anorexia. Bone marrow AEs included neutropenia, thrombocytopenia and anemia. AEs were evaluated using an objective scoring system derived from the VOCG-CTCAE (Tables 1 and 2). Gastrointestinal AEs were assessed 1 or 2 weeks after administration of the chemotherapy agent, based on the clinical signs. Bone marrow AEs were assessed 1 or 2 weeks after the administration of the chemotherapeutic agent; the exception were dogs admitted before their scheduled appointments due to apparent changes in general condition. All dogs underwent complete blood cell counts (CBCs) immediately before chemotherapy treatment. Dogs with gastrointestinal signs (anorexia, diarrhea, vomiting) or CBC abnormalities (anemia, neutropenia, thrombocytopenia) prior to chemotherapy were excluded from the assessment of chemotherapeutic AEs.

### Statistical analysis

The prevalence of dogs that experienced gastrointestinal and bone marrow AEs after chemotherapy were compared using the chi-square and Fisher's exact tests. For all analyses, a $P$-value < 0.05 was considered significant. Statistical analysis was performed using SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA).

## Results

### Baseline characteristics of the dogs

This retrospective study examined 42 dogs diagnosed with malignant tumors. The 42 dogs included 11 intact males, 15 neutered males, 14 intact females, and 2 spayed females. The Maltese (n = 9) and Shih Tzu (n = 9) were the most common breeds represented. Other breeds included were the Miniature Schnauzer (n = 5), Cocker Spaniel (n = 3), Golden Retriever (n = 2), Rottweiler (n = 1), Sapsali (n = 1), Old English Sheepdog (n = 1), Labrador Retriever (n = 1), Kerry Blue Terrier (n = 1), Pug (n = 1), Samoyed (n = 1), Miniature Poodle (n = 1), Yorkshire Terrier (n = 1), Welsh Corgi (N = 1), and Pomeranian (n = 1). Three dogs were mixed-breed. The dogs were aged 9 months to 18 years; the median age was 10.3 ± 4.3 years. The body weights were between

**Table 3.** The number of dogs that experienced adverse events 1 or 2 weeks after VCR administration

| Number of administration | Number of dogs receiving chemotherapy | Number of dogs that experienced gastrointestinal adverse events (%) | Gastrointestinal adverse events (Anorexia, Diarrhea, Vomiting) | | | | | Number of dogs that experienced bonemarrow adverse events (%) | Blood/bone marrow adverse events (Anemia, Neutropenia, Thrombocytopenia) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Grade | | | | | | Grade | | | | |
| | | | 1 | 2 | 3 | 4 | 5 | | 1 | 2 | 3 | 4 | 5 |
| 1 | 28 | 11 (39.3%) | 11 | - | - | - | - | 0 (0%) | - | - | - | - | - |
| 2 | 18 | 0 (0%) | - | - | - | - | - | 2 (11.1%) | 2 | - | - | - | - |
| 3 | 14 | 3 (21.4%) | 2 | 1 | - | - | - | 1 (7.1%) | 1 | - | - | - | - |
| 4 | 13 | 0 (0%) | - | - | - | - | - | 2 (11.1%) | 2 | - | - | - | - |
| 5 | 13 | 3 (21.4%) | 3 | - | - | - | - | 0 (0%) | - | - | - | - | - |
| 6 | 13 | 0 (0%) | - | - | - | - | - | 0 (0%) | - | - | - | - | - |
| 7 | 10 | 0 (0%) | - | - | - | - | - | 0 (0%) | - | - | - | - | - |
| 8 | 10 | 0 (0%) | - | - | - | - | - | 0 (0%) | - | - | - | - | - |

VCR; vincristine.

2.2 kg and 33.4 kg; the median body weight was 9.6 ± 8.5 kg.

**Chemotherapy-related gastrointestinal and bone marrow AEs**

VCR-related adverse events

Twenty-eight dogs were treated with VCR per lymphoma chemotherapy protocol UW-25. The prevalence and severity of gastrointestinal and bone marrow AEs were evaluated according to the frequency of VCR administration (Table 3). During VCR chemotherapy, 12 of the 28 dogs (42.9%) experienced at least one gastrointestinal AE, and 4 of 28 (14.3%) experienced at least one bone marrow AE. The gastrointestinal AEs were grade 1 and grade 2 severity. The bone marrow AEs were grade 1 severity. Sixteen of the 28 dogs (57.1%) did not experience gastrointestinal or bone marrow AEs after VCR administration. Of the 12 dogs that experienced gastrointestinal and/or bone marrow AEs due to VCR, the dose for one dog was reduced by 14% due to toxicity; the dog did not experience additional AEs after dose reduction.

CP-related adverse events

Twenty-three dogs were administered CP to treat lymphoma per chemotherapy protocol UW-25. The prevalence and severity of the gastrointestinal and bone marrow AEs were evaluated according to the frequency of CP administration (Table 4). During treatment with CP, 9 of the 23 dogs (39.1%) experienced at least one gastrointestinal AE, and 8 of 23 (34.8%) experienced at least one bone marrow AE. The severity of the gastrointestinal and bone marrow AEs was grade 1 or grade 2. Nine of the 23 dogs (39.1%) did not experience gastrointestinal or bone marrow AEs after administration of CP. Of the 14 dogs that experienced gastrointestinal and/or bone marrow AEs due to CP, the dose for 2 dogs was reduced by 20%; the dogs did not develop AEs after dose reduction.

DOX-related adverse events

Eighteen dogs with lymphoma and 2 dogs with hemangiosarcoma were treated with DOX. The prevalence and severity of gastrointestinal and bone marrow AEs were evaluated according to the frequency of DOX administration (Table 5). During DOX treatment, 9 of the 20 dogs (45%) experienced at least one gastrointestinal AE, and 4 of 20 patients (20%) experienced at least one bone marrow AE. The severity of the gastrointestinal AEs was grade 1 or grade 2. The severity of all bone marrow AEs was grade 1. Eleven of the 20 dogs (55%) did not experience gastrointestinal or bone marrow AEs after DOX administration. Of 9 dogs that experienced gastrointestinal and/or bone marrow AEs, the dose administered to 1 dog was reduced by 20%. The dog did not develop AEs after dose reduction.

Lomustine-related adverse events

Lomustine was administrated to 9 dogs with lymphoma, 2 dogs with hepatocellular carcinoma, 2 dogs with meningioma, and 1 dog with choroid plexus papilloma. The prevalence and severity of gastrointestinal and bone marrow AEs were evaluated according to the frequency of lomustine

**Table 4.** The number of dogs that experienced adverse events 1 or 2 weeks after CP administration

| Number of administration | Number of dogs receiving chemotherapy | Number of dogs that experienced gastrointestinal adverse events (%) | Gastrointestinal adverse events (Anorexia, Diarrhea, Vomiting) | | | | | Number of dogs that experienced bonemarrow adverse events (%) | Blood/bone marrow adverse events (Anemia, Neutropenia, Thrombocytopenia) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Grade | | | | | | Grade | | | | |
| | | | 1 | 2 | 3 | 4 | 5 | | 1 | 2 | 3 | 4 | 5 |
| 1 | 23 | 5 (21.7%) | 5 | - | - | - | - | 5 (21.7%) | 4 | 1 | - | - | - |
| 2 | 13 | 2 (15.4%) | 1 | 1 | - | - | - | 6 (46.2%) | 6 | - | - | - | - |
| 3 | 13 | 3 (23.1%) | 3 | - | - | - | - | 0 (0%) | - | - | - | - | - |
| 4 | 11 | 0 (0%) | - | - | - | - | - | 1 (9.1%) | 1 | - | - | - | - |

CP; cyclophosphamide.

**Table 5.** The number of dogs that experienced adverse events 1 or 2 weeks after DOX administration

| Number of administration | Number of dogs receiving chemotherapy | Number of dogs that experienced gastrointestinal adverse events (%) | Gastrointestinal adverse events (Anorexia, Diarrhea, Vomiting) | | | | | Number of dogs that experienced bonemarrow adverse events (%) | Blood/bone marrow adverse events (Anemia, Neutropenia, Thrombocytopenia) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Grade | | | | | | Grade | | | | |
| | | | 1 | 2 | 3 | 4 | 5 | | 1 | 2 | 3 | 4 | 5 |
| 1 | 20 | 5 (25%) | 4 | 1 | - | - | - | 3 (15%) | 3 | - | - | - | - |
| 2 | 14 | 4 (28.6%) | 2 | 2 | - | - | - | 2 (14.3%) | 2 | - | - | - | - |
| 3 | 13 | 1 (7.7%) | 1 | - | - | - | - | 1 (7.7%) | 1 | - | - | - | - |
| 4 | 11 | 2 (18.2%) | 2 | - | - | - | - | 0 (0%) | - | - | - | - | - |

DOX; doxorubicin.

**Table 6.** The number of dogs that experienced adverse events 1 or 2 weeks after lomustine administration

| Number of administration | Number of dogs receiving chemotherapy | Number of dogs that experienced gastrointestinal adverse events (%) | Gastrointestinal adverse events (Anorexia, Diarrhea, Vomiting) | | | | | Number of dogs that experienced bonemarrow adverse events (%) | Blood/bone marrow adverse events (Anemia, Neutropenia, Thrombocytopenia) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Grade | | | | | | Grade | | | | |
| | | | 1 | 2 | 3 | 4 | 5 | | 1 | 2 | 3 | 4 | 5 |
| 1 | 14 | 4 (28.6%) | 4 | - | - | - | - | 8 (57.1%) | 7 | - | - | 1 | - |
| 2 | 12 | 1 (8.3%) | 1 | - | - | - | - | 4 (33.3%) | 4 | - | - | - | - |
| 3 | 9 | 0 (0%) | - | - | - | - | - | 2 (22.2%) | 2 | - | - | - | - |
| 4 | 6 | 0 (0%) | - | - | - | - | - | 2 (33.3%) | 2 | - | - | - | - |
| 5 | 5 | 1 (20%) | 1 | - | - | - | - | 2 (40%) | 2 | - | - | - | - |
| 6 | 5 | 1 (20%) | 1 | - | - | - | - | 3 (60%) | 2 | - | - | 1 | |
| 7 | 3 | 0 (0%) | - | - | - | - | - | 1 (33.3%) | 1 | - | - | - | - |
| 8 | 2 | 0 (0%) | - | - | - | - | - | 1 (50%) | 1 | - | - | - | - |

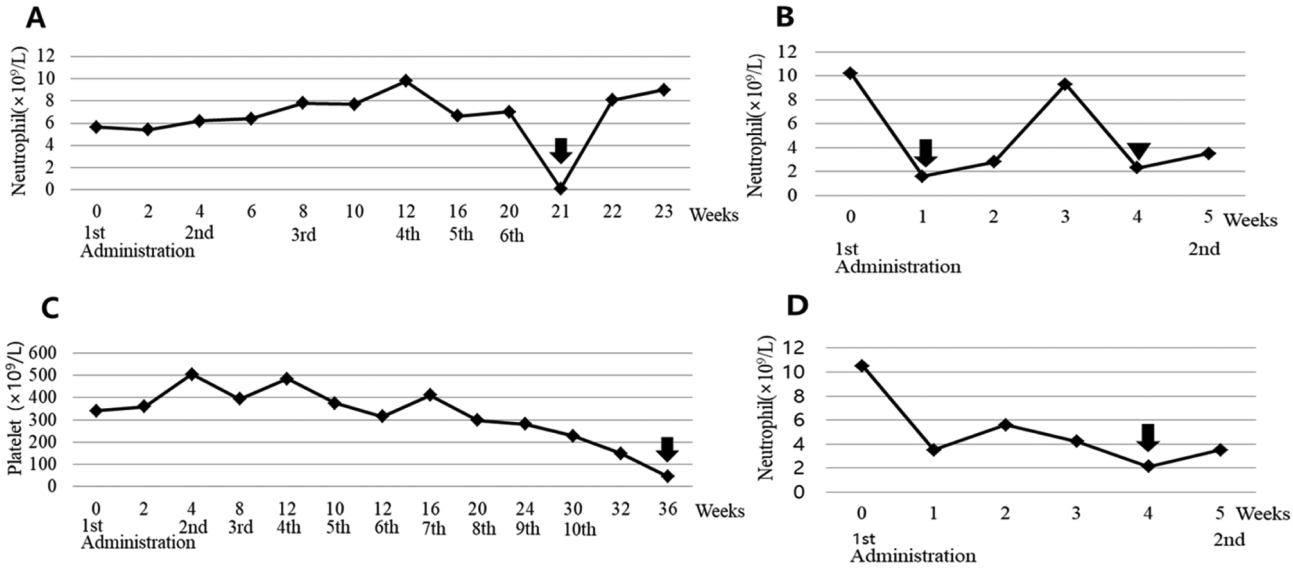


**Fig 1.** Delayed and cumulative bone marrow AEs due to lomustine chemotherapy. (A) Grade 4 neutropenia ($0.48 \times 10^9$ / L) was identified 1 week after the sixth administration of lomustine in this dog (arrow). (B) Grade 1 neutropenia occurred 1 week ($1.6 \times 10^9$ / L, arrow) and 4 weeks ($2.3 \times 10^9$ / L, arrowhead) after the first administration of lomustine in this dog. (C) Grade 3 ($44 \times 10^9$ / L) thrombocytopenia was identified 6 weeks after tenth administration of lomustine in this dog (arrow). (D) This dog experienced grade 1 neutropenia ($0.48 \times 10^9$ / L), 4 weeks after the first administration of lomustine (arrow).

administration (Table 6). During lomustine treatment, 4 of the 14 dogs (28.6%) experienced at least one gastrointestinal AE, and 10 of 14 (71.4%) experienced at least one bone marrow AE. The severity of all gastrointestinal AEs was grade 1. Bone marrow AEs of both grade 1 and grade 4 severity were observed. Four of the 14 dogs (28.6%) did not experience gastrointestinal or bone marrow AEs after administration of lomustine. Of 10 dogs that experienced gastrointestinal and/or bone marrow AEs, the dose for 2 dogs was reduced by 8.6% and 14.3%. The dog that received the dose reduction of 14.3% did not develop additional AEs, but the dog that received the dose reduction of 8.6% experienced toxicities despite the reduced dose.

Some dogs that received regular blood tests after administration of lomustine had no evidence of bone marrow AEs, and then severe bone marrow AEs (grade 3 thrombocytopenia and grade 4 neutropenia) were identified. In addition, some bone marrow AEs were observed 4 or 6 weeks after the lomustine administration (Fig 1).

### Carboplatin-related adverse events

Carboplatin was used to treat transitional cell carcinoma (n = 4), hepatic tumor (n = 2), gastric tumor (n = 1), colon tumor (n = 1), and rectal adenocarcinoma (n = 1). The prevalence and severity of gastrointestinal and bone marrow AEs were evaluated according to the frequency of carboplatin administration (Table 7). During treatment with carboplatin, 6 of the 9 dogs (66.7%) experienced at least one gastrointestinal AEs, and 4 of 9 (44.4%) experienced at least one bone marrow AE. The severity of the gastrointestinal AEs was grade 1 or grade 2. The severity of the bone marrow AEs was grade 1 or grade 3. Two of the 9 dogs (22.2%) did not

**Table 7.** The number of dogs that experienced adverse events 1 or 2 weeks after carboplatin administration

| Number of administration | Number of dogs receiving chemotherapy | Number of dogs that experienced gastrointestinal adverse events (%) | Gastrointestinal adverse events (Anorexia, Diarrhea, Vomiting) | | | | | Number of dogs that experienced bonemarrow adverse events (%) | Blood/bone marrow adverse events (Anemia, Neutropenia, Thrombocytopenia) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Grade | | | | | | Grade | | | | |
| | | | 1 | 2 | 3 | 4 | 5 | | 1 | 2 | 3 | 4 | 5 |
| 1 | 9 | 4 (44.4%) | 3 | 1 | - | - | - | 3 (15%) | 3 | 1 | - | - | - |
| 2 | 5 | 2 (40%) | 2 | - | - | - | - | 2 (14.3%) | 2 | - | - | - | - |
| 3 | 3 | 0 (0%) | - | - | - | - | - | 1 (7.7%) | - | - | - | - | - |

develop gastrointestinal or bone marrow AEs after administration of carboplatin. Seven dogs experienced gastrointestinal and/or bone marrow AEs; the dose for one dog was reduced by 20%, and that dog did not experience additional AEs.

**Comparison of the prevalence of dogs that experienced chemotherapy-related gastrointestinal and bone marrow adverse events**

We compared the prevalence of dogs that experienced gastrointestinal and bone marrow AEs due to VCR, CP, DOX, lomustine, and carboplatin. The prevalence of dogs that experienced gastrointestinal AEs due to VCR, CP, DOX, lomustine, or carboplatin was 42.9%, 39.1%, 45%, 28.6%, and 66.7%, respectively. However, there were no significant differences in the prevalence of gastrointestinal AEs among the 5 chemotherapeutic agents ($P = 0.49$). The prevalence of bone marrow AEs due to VCR, CP, DOX, lomustine, or carboplatin was 14.3%, 34.8%, 20%, 71.4%, and 44.4%, respectively. The prevalence of bone marrow AEs was significantly higher after administration of lomustine than after administration of VCR (odd ration [OR] = 15.00, $P = 0.00041$) or DOX (odd ration [OR] = 10.00, $P = 0.003$).

**Severity of chemotherapy-related gastrointestinal and bone marrow adverse events**

Twelve dogs experienced gastrointestinal and/or bone marrow AEs after administration of VCR. Of the 12, 8 experienced only gastrointestinal AEs and 4 experienced both gastrointestinal and bone marrow AEs. Of the dogs that experienced only gastrointestinal AEs, 7 dogs experienced grade 1 AEs and 1 experienced a grade 2 AE. All AEs of the 4 dogs with both gastrointestinal and bone marrow were grade 1.

Among 14 dogs that experienced gastrointestinal and/or bone marrow AEs after administration of CP, 6 experienced only gastrointestinal AEs, 3 experienced both gastrointestinal and bone marrow AEs, and 5 experienced only bone marrow AEs. Five dogs in the group of only gastrointestinal AEs, 3 dogs in the group of both gastrointestinal and bone marrow AEs, and 4 dogs in the group of only bone marrow AEs group had grade 1 AEs. A grade 2 AE was observed in 1 dog in the group of only gastrointestinal AEs and in 1 dog in the group of only bone marrow AEs.

Of 9 dogs that experienced gastrointestinal or/and bone marrow AEs after administration of DOX, 5 experienced only gastrointestinal AEs and 4 experienced both gastrointestinal and bone marrow AEs. Three dogs that experienced only gastrointestinal AEs, and 4 that experienced both gastrointestinal and bone marrow AEs, had grade 1 AEs. Two dogs that experienced only gastrointestinal AEs had grade 2 AEs.

Among 10 dogs that experienced gastrointestinal and/or bone marrow AEs after administration of lomustine, 6 experienced only bone marrow AEs and 4 experienced both gastrointestinal and bone marrow AEs. Two dogs that experienced only bone marrow AEs had grade 4 AEs. The remaining 6 dogs all experienced grade 1 AEs.

Of 7 dogs that experienced gastrointestinal and/or bone marrow AEs after administration of carboplatin, 3 experienced only gastrointestinal AEs, 3 experienced both gastrointestinal and bone marrow AEs, and 1 experienced only bone marrow AEs. Grade 1 AEs were observed in 2 dogs in the group of only gastrointestinal AEs and 3 dogs in the group of both gastrointestinal and bone marrow AEs. A grade 2 gastrointestinal AE was in 1 dog in the group of only gastrointestinal AEs, and a grade 3 bone marrow AE was observed in 1 dog in the group of only gastrointestinal AEs.

In this study, grade 1 AEs of the gastrointestinal tract and bone marrow were most often observed after administration of various chemotherapeutic agents. Grade 3 and grade 4 bone marrow AEs occurred in dogs receiving carboplatin and lomustine, respectively.

## Discussion

Cytotoxic chemotherapeutic agents affect all rapidly dividing cells; they cannot distinguish rapidly diving normal cells from tumor cells. Thus, transitional cytotoxic chemotherapeutic agents have side effects including gastrointestinal problems (vomiting, diarrhea, anorexia), bone marrow suppression (neutropenia, thrombocytopenia, anemia), and alopecia (13). Chemotherapy-induced alopecia appears to be cosmetic and does not negatively impact the QOL of the dogs (14). Therefore, we did not evaluate alopecia after chemotherapy.

Gastrointestinal toxicities may range from mild to severe depending on the patient. Gastrointestinal toxicities with a severity of grade 3 or higher were observed after chemotherapy in previous studies of gastrointestinal AEs; these toxicities were self-limiting and did not require special treatments (4,12,25). However, severe gastrointestinal signs that required hospitalization or that related in death were reported in other studies (8,9,19). In this retrospective study, most gastrointestinal AEs due to various chemotherapeutic agents were grade 1. If clinical signs associated with gastrointestinal AEs due to

tumor or other disease progression were present before chemotherapy, we excluded the case from the assessment of gastrointestinal toxicity. Dogs that experienced vomiting after a previous chemotherapy session were prophylactically treated with antiemetics at the next session. Previous studies showed that maropitant effectively reduced or prevented chemotherapy-induced vomiting, and prophylactic use of maropitant may improve the QOL and decrease the need for subsequent dose reductions of chemotherapeutic agents in certain patients (20,23). These reasons may help explain why most of the gastrointestinal AEs due to 5 different chemotherapeutic agents in this study were mild.

In the present study, gastrointestinal AEs were evaluated 1 or 2 weeks after administration of the chemotherapeutic agent, according to the chemotherapy schedule. The prevalence of gastrointestinal AEs was recorded based on the clinical signs described by the owner at the next session or during a telephone follow-up. Vomiting is due to damage of the rapidly dividing crypts cells of the gastrointestinal tract or to stimulation of the chemoreceptor trigger zone. In the former case, vomiting occurs 3 to 5 days after chemotherapy; in the latter case, it usually occurs during drug administration or soon after chemotherapy (10). In this study, the most common gastrointestinal AE was vomiting, which occurred within 1 week. Therefore, the changes in the evaluation intervals conceivably did not influence the incidence rate of gastrointestinal AEs. The neutrophil nadir in small animals generally occurs 5-10 days after chemotherapy (13), and most animals received a follow-up CBC 1 week after treatment. However, some animals were evaluated 2 weeks after chemotherapy because the client was not able to visit at 1 week. However, some patients were evaluated 2 weeks after chemotherapy because client did not visit at 1 week. The timing of the absolute nadir also varies depending on the individual animal (18). Therefore, a single CBC nadir may not represent the dog's absolute nadir, even though blood examination was performed at the same time as in another dog. For these reasons, this study may have underestimated the occurrence of bone marrow AEs after chemotherapy.

Nitrosourea pharmaceuticals such as lomustine have the unique property of delayed, cumulative bone marrow suppression. The nadir of neutrophil counts occurs 3-4 weeks after administration and the nadir of platelet counts occurs 4-5 weeks after chemotherapy (24). However, the ease of lomustine oral administration may have decreased the client's perception of the dog's risk of development of side effects after chemotherapy, or previous long-term chemotherapy without significant problems reduced the perceived need for regular blood tests. For these reasons, some owners often did not obtain a CBC after each treatment. Therefore, it may be difficult to identify delayed, cumulative bone marrow suppression of lomustine, and some previous studies have reported that bone marrow suppression due to lomustine was not identified (7,15). Although we did not perform blood tests every week in all dogs receiving lomustine due to the limitations mentioned above, we identified delayed and cumulative myelosuppression of lomustine in some dogs receiving regular CBCs; two of those dogs experienced severe bone marrow AEs. Therefore, careful monitoring of hematologic data and clinical signs is warranted during prolonged lomustine administration.

In this retrospective study, some dogs experienced gastrointestinal and/or bone marrow AEs after administration of various chemotherapeutic agents; others did not. Possible reasons for this difference include differences in the activity of the hepatic metabolic enzymes and differences in kidney function. VCR and DOX are metabolized predominantly by the liver and are excreted in the bile. If these chemotherapeutic agents must be used, the dose should be decreased by 50% to reduce toxicity. CP and carboplatin are excreted by the kidneys, and the dose should be reduced if the serum creatinine level is elevated due to renal disease (14). It has been reported that in humans, VCR is selectively metabolized by CYP3A5, which may be a major determinant in the P450-mediated clearance of VCR (5). Analysis of the polymorphism of the liver enzyme and the presence of liver and kidney disease will help predict the possibility of adverse events after the administration of various chemotherapeutic agents. However, in veterinary medicine, there is a lack of study of the genetic polymorphisms of metabolic enzymes. Further studies of the pharmacokinetics of chemotherapeutic agents in dogs are necessary to understand and predict the AEs of chemotherapeutic agents.

The gastrointestinal and/or bone marrow AEs of various chemotherapeutic agents at the doses used in this study were acceptable; few dogs required dose reductions, and there were no treatment-related deaths. The dogs that experienced gastrointestinal and bone marrow toxicities before chemotherapy were excluded from evaluation of chemotherapy-related AEs in this study. However, some animals with clinical symptoms and CBC abnormalities before chemotherapy may have had more severe toxicities after chemotherapy. Therefore, veterinarians must be aware that severe gastrointestinal and/or bone marrow AEs may be identified in dogs that had gastrointestinal signs or/and CBC abnormalities before chemotherapy, and should monitor these dogs more carefully.

The serious or uncontrolled AEs of chemotherapeutic drugs may decrease the QOL of dogs, delay treatment, or reduce the dose of chemotherapeutic drugs, which may decrease the effectiveness of chemotherapy. A reduction of the dose of a chemotherapeutic drug by 20% has been reported to reduce the effect of treatment by 50% (13). In addition, clients often believe that their pet is experiencing unnecessary toxicities, which may result in abandonment of life-saving treatment and subsequent euthanasia. Therefore, the veterinarian must explain to clients the types and likelihood of AEs that may occur in their companion animals, and should plan for preventative and therapeutic protocols to effectively manage those AEs (21).

This study has some limitations. First, the population of animals receiving chemotherapy was small compared to that in previous studies. The small sample size resulted in limited statistical power and the inability to statistically assess the prevalence of AEs according to an increase in the administration frequency of chemotherapeutic agents. Second, we did not evaluate the AEs of chemotherapy depending on the dosage used and interval of administration. Third, serum chemistry and ultrasound examination after chemotherapy were

not performed in all animals. Thus, we did not evaluate various AEs of chemotherapeutic agents such as hepatotoxicity and renal toxicity. Based on the VCOG-CTCAE, we evaluated only gastrointestinal and bone marrow AEs, which are common after chemotherapy (13,14). The veterinary cooperative oncology group classified the various categories, defined the terminology, and divided the grades of AEs after chemotherapy in dogs (22). The toxicities of chemotherapy may vary depending on the dose of the drug, the interval of administration, and the animal's condition (13). Therefore, it is necessary to evaluate individual animals, and additional studies are needed to evaluate the various AEs of chemotherapeutic agents using an objective evaluation system.

In conclusion, the present study reported the prevalence and severity of gastrointestinal and bone marrow AEs after administration of various chemotherapeutic agents in canines with malignant tumors based on the objective grading system of the VOCG-CTCAE. The results of this study showed that gastrointestinal and bone marrow AEs of these chemotherapeutic agents were common, but these agents were generally well-tolerated and had acceptable toxicities. However, delayed and cumulative myelosuppression of lomustine may occur, and may be severe. Therefore, careful monitoring of hematologic data and clinical signs is necessary with prolonged lomustine treatment.

The findings of this study will help predict possible gastrointestinal and bone marrow AEs due to the use of chemotherapeutic agents to treat canines with malignant tumors.

## Acknowledgement

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2017R1D1A1B03034904).

## References

1. Blachley JD, Hill JB. Renal and electrolyte disturbances associated with cisplatin. Ann Intern Med 1981; 95: 628-632.
2. Bregazzi VS, LaRue SM, McNiel E, Macy DW, Dernell WS, Powers BE, Withrow SJ. Treatment with a combination of doxorubicin, surgery, and radiation versus surgery and radiation alone for cats with vaccine-associated sarcomas: 25 cases (1995-2000). J Am Vet Med Assoc 2001; 218: 547-550.
3. Chun R, Garrett L, Vail D. Cancer Chemotherapy. In: Small Animal Clinical Oncology, 4 th ed. St. Louis: Saunders Elsevier. 2007: 163-192.
4. Chun R, Knapp DW, Widmer WR, DelNicola DB, Glickman NW, Kuczek T, Degortari A, Han CM. Phase II clinical trial of carboplatin in canine transitional cell carcinoma of the urinary bladder. J Vet Intern Med 1997; 11: 279-283.
5. Dennison JB, Jones DR, Renbarger JL, Hall SD. Effect of CYP3A5 expression on vincristine metabolism with human liver microsomes. J Pharmacol Exp Ther 2007; 321: 553-563.
6. Eschalier A, Lavarenne J, Burtin C, Renoux M, Chapuy E, Rodriguez M. Study of histamine release induced by acute administration of antitumor agents in dogs. Cancer Chemother Pharmacol 1988; 21: 246-250.
7. Fan TM, Kitchell BE, Dhaliwal RS, Jones PD, Hintermeister JG, Paria BC. Hematological toxicity and therapeutic efficacy of lomustine in 20 tumor-bearing cats: critical assessment of a practical dosing regimen. J Am Anim Hosp Assoc 2002; 38: 357-363.
8. Hammer AS, Couto CG, Filppi J, Getzy D, Shank K. Efficacy and toxicity of VAC chemotherapy (vincristine, doxorubicin, and cyclophosphamide) in dogs with hemangiosarcoma. J Vet Intern Med 1991; 5: 160-166.
9. Heading K, Brockley L, Bennett P. CCNU (lomustine) toxicity in dogs: a retrospective study (2002-07). Aust Vet J 2011; 89: 109-116.
10. Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl Med 2008; 358: 2482-2494.
11. Kristal O, Rassnick KM, Gliatto JM, Northrup NC, Chretin JD, Morrison?Collister K, Cotter SM, Moore AS. Hepatotoxicity associated with CCNU (lomustine) chemotherapy in dogs. J Vet Intern Med 2004; 18: 75-80.
12. Lori J, Stein T, Thamm D. Doxorubicin and cyclophosphamide for the treatment of canine lymphoma: a randomized, placebo-controlled study. Vet Comp Oncol 2010; 8: 188-195.
13. MacDonald V. Chemotherapy: managing side effects and safe handling. Can Vet J 2009; 50: 665.
14. McKnight JA. Principles of chemotherapy. Clin Tech Small Anim Pract 2003; 18: 67-72.
15. Moore AS, London CA, Wood CA, Williams LE, Cotter SM, L'Heureux DA, Frimberger AE. Lomustine (CCNU) for the treatment of resistant lymphoma in dogs. J Vet Intern Med 1999; 13: 395-398.
16. Noda T, Watanabe T, Kohda A, Hosokawa S, Suzuki T. Chronic effects of a novel synthetic anthracycline derivative (SM-5887) on normal heart and doxorubicin-induced cardiomyopathy in beagle dogs. Invest New Drugs 1998; 16: 121-128.
17. O'Keefe DA, Sisson DD, Gelberg HB, Schaeffer DJ, Krawiec DR. Systemic toxicity associated with doxorubicin administration in cats. J Vet Intern Med 1993; 7: 309-317.
18. Rassnick KM, Gieger TL, Williams LE, Ruslander DM, Northrup NC, Kristal O, Myers NC, Moore AS. Phase I evaluation of CCNU (Lomustine) in tumor-bearing cats. J Vet Intern Med 2001; 15: 196-199.
19. Rassnick KM, Ruslander DM, Cotter SM, Al-Sarraf R, Bruyette DS, Gamblin RM, Meleo KA, Moore AS. Use of carboplatin for treatment of dogs with malignant melanoma: 27 cases (1989-2000). J Am Vet Med Assoc 2001; 218: 1444-1448.
20. Rau S, Barber L, Burgess K. Efficacy of maropitant in the prevention of delayed vomiting associated with administration of doxorubicin to dogs. J Vet Intern Med 2010; 24: 1452-1457.
21. Vail DM. Supporting the veterinary cancer patient on chemotherapy: neutropenia and gastrointestinal toxicity. Top Companion Anim Med 2009; 24: 122-129.
22. Vale D. Veterinary co-operative oncology group-common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats. Vet Comp Oncol 2004; 2: 194-213.
23. Victor A, Tilt N, Rowan TG, Clemence RG. Efficacy of maropitant for treatment and prevention of emesis caused by intravenous infusion of cisplatin in dogs. Am J Vet Res 2007; 68: 48-56.
24. Weiss RB, Issell BF. The nitrosoureas: carmustine (BCNU) and lomustine (CCNU). Cancer Treat Rev 1982; 9: 313-330.
25. Williams LE, Rassnick KM, Power HT, Lana SE, Morrison-Collister KE, Hansen K, Johnson JL. CCNU in the treatment of canine epitheliotropic lymphoma. J Vet Intern Med 2006; 20: 136-143.