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Febrile Neutropenia in 523 Dogs with Various Malignant Tumors

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Febrile Neutropenia (FN)

- Fever and neutropenia caused by chemotherapy
- One of the severe side effects of chemotherapeutic agents
- Caused by Vincristine and Doxorubicin most commonly

Sorenmo KU, JAVMA, 2010
Britton BM, Vet Comp Oncol, 2013

Our study objective

- To evaluate FN that occurred after administration of the following chemotherapeutic agents
  - Carboplatin (CBDCA)
  - Cyclophosphamide (CPM)
  - Doxorubicin (DOX)
  - Vincristine (VCR)
  - Mitoxantorone (MIT)
  - Lomustine (CCNU)

Methods

Inclusion criteria

- Dogs that received chemotherapy at JSACC between Jan/2005 and June/2012

Exclusion criteria

- Dogs that could not be followed more than 6 days after chemotherapy
- Dogs that received more than one agent at the same time

Definition of FN

- Neutrophil count < 2500 cells/μL
- Body temperature > 39.2℃ or < 36.0℃

Sorenmo KU, JAVMA, 2010
Britton BM, Vet Comp Oncol, 2013
VCOG-CTCAE ver1.1 Vet Comp Oncol. 2011

Data analyses

Overall incidence rate of FN

- Incidence of FN / Total number of chemotherapy ×100

Overall mortality of FN

- Total number of all deaths / Total number of all dogs×100

Mortality rate of FN

- Total number of all deaths / Total number of FN ×100

Analysis of risk factors

Factors

- Age (< 8y vs. ≧ 8y)
- Sex (male vs. female)
- Body weight (<10kg vs. ≧10kg)

Statistical analysis

- Logistic model ($p<0.05$)

Results

Dogs characteristics

Median age: 9 years old (1-17)

Median BW: 10.6 kg (1.9-63.3)

Sex :

- Female 258 (neutered 162), Male 265 (neutered 121)

Tumor type :

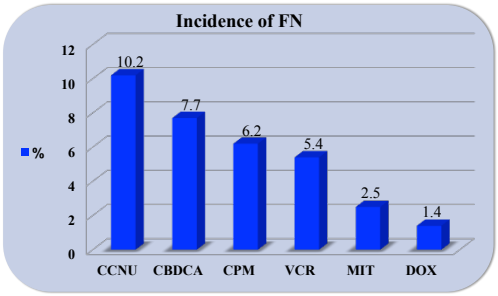
- Lymphoma or Leukemia : 327
- Solid tumors : 196
  - Histiocytic sarcoma: 44
  - Mast cell tumor: 19
  - Hemangiosarcoma: 19
  - Others: 114

Numbers of dogs / Dosed of drugs

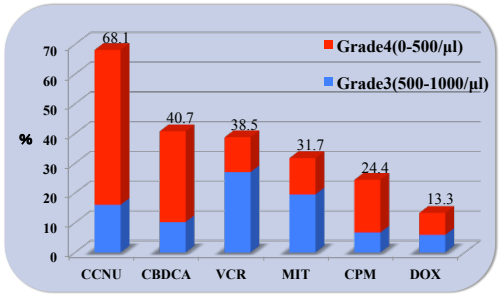
Drug	Number (chemo)	Dosage (range)	Dose (mode)
CBDCA	59 (168)	150 – 300 mg/m²	250 mg/m²
CPM	90 (241)	150 – 250 mg/m²	250 mg/m²
DOX	135 (425)	1 mg/kg – 30mg/m²	1mg/kg
VCR	104 (484)	0.35 – 0.7mg/m²	0.7 mg/m²
MIT	41 (118)	3.75 –5.5 mg/m²	5 mg/m²
CCNU	94 (334)	44 – 87.7 mg/m²	70.0 mg/m²*

※ median

Overall Incidence of FN = 5.5% (97/1770)



Incidence rate of > Grade 3 neutropenia



VCOG-CTCAE ver1.1. Vet Comp Oncol. 2011

Mortality rate

- Overall mortality rate = 0.95% (5/523)
- Mortality rate of FN = 5.88% (5/85)

Summary of dogs that died

Dogs	BW(kg)	Drug	Tumor	Region	Lung lesion	GI sign	Seg (μ/L)
W.Corgie	15.4	CCNU 70.9 mg/m²	HS	Liver LN	+	+	57
Shih tzu	5.54	CCNU 63.3 mg/m²	LSA	skin	-	-	43
Shelty	14.3	CBDCA 250 mg/m²	LSA	Multicentric LN	+	+	1223
M.Dachs	5.68	CBDCA 250 mg/m²	TCC	Bladder	+	+	71
W.Corgie	15.08	CPM 250 mg/m²	LSA	Multicentric LN (CR)	-	-	672

Analysis of risk factors

- Age : p=0.700
- Sex : p=0.194
- BW : p=0.401

Discussion

Comparison with the previous study

Drugs	Previous report (n=70)	Our study (n=85)
DOX	37.1 % (26)	7.0 % (6)
VCR	32.9 % (23)	28.2 % (24)
CPM	22.8 % (16)	15.2 % (13)
CCNU	12.8 % (9)	30.5 % (26)
CBDCA	5.7 % (4)	15.2 % (13)
MIT	-	3.5 % (3)

Britton BM, Vet Comp Oncol, 2013

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Britton BM, Vet Comp Oncol, 2013

Relationship between dose of DOX and BW

< 5 kg : 1mg/kg
5 – 10 kg : 20 ~ 25mg/m^2
10 –15 kg : 25 ~ 30mg/m^2
> 15 kg : 30mg/m^2

Relationship between dose of DOX and BW

< 5 kg : 1mg/kg → 20% (27/135)
5 – 10 kg : 20 ~ 25mg/m^2 → 35.5% (48/135)
10 –15 kg : 25 ~ 30mg/m^2 → 17.7% (24/135)
> 15 kg : 30mg/m^2 → 26.6% (36/135)

Comparison with mortality rate in two studies

- Previous study = 8.57%
- Our study =5.88%

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Risk factors of FN in human

Rate of severe FN < 5%

Risk factors (high risk)

- Pulmonary infiltration or chronic lung disease
- GI signs (abdominal pain, nausea, vomiting and diarrhea)
- GI mucosal disorder with dysphasia or diarrhea
- Severe neutropenia (<100cells/μL) for more than 7 days
- Intravascular catheter infection
- New or worsening neurological disorders

American Society of clinical oncology / European society for medical Oncology

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Our future directions

- To investigate the risk factors that could cause side effects in each agent
- To investigate the appropriate dosage for small breeds