

Mycobacterium Cell Wall-DNA complex (MCW-DNA) as an aid in the treatment of chemotherapy-induced neutropenia in healthy dogs

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Introduction

- There is an unmet need to provide improved management of adverse events following the use of chemotherapeutics in veterinary oncology patients.
- *Specifically, there is a lack of supportive veterinary products for the management of myelosuppression and the associated hematological adverse events (especially neutropenia), observed in dogs undergoing chemotherapy.*
- *Myelosuppression, defined as a "condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets", is frequently documented during active treatment of canine cancers with commonly used chemotherapeutic drugs.*
- **Neutropenia** is the most common blood/bone marrow adverse event in chemotherapy protocols.
- **Vinblastine (VBL)** and similar vinca-alkaloid chemotherapeutics have been commonly used to treat canine cancers. Majority of these drugs are NOT approved for veterinary use.
- **Higher dose treatments of a single chemotherapeutic drug or drug combinations are associated with increased severity of neutropenia.**

MCW-DNA composition

- MCW-DNA - mycobacterial cell wall fraction; composition derived from *Mycobacterium phlei* (*M. phlei*).
- *M. phlei* is a **nonpathogenic**, gram-positive, ubiquitous bacteria commonly found in the environment, soil, dust and on the leaves of plants.
- MCW-DNA contains mycobacterial cell wall complexed with nucleic acid (DNA and RNA)
- MCW-DNA formulation used in final phase III clinical trials for the treatment of human bladder cancer (refractory patients)
- Veterinary side: MCW formulations are registered products (USA, CA, AUS, NZ) for different indications in equine, bovine and canine species.
- Immunocidin®-MCW formulation for treatment of mixed mammary tumors and mammary adenocarcinoma in dogs.

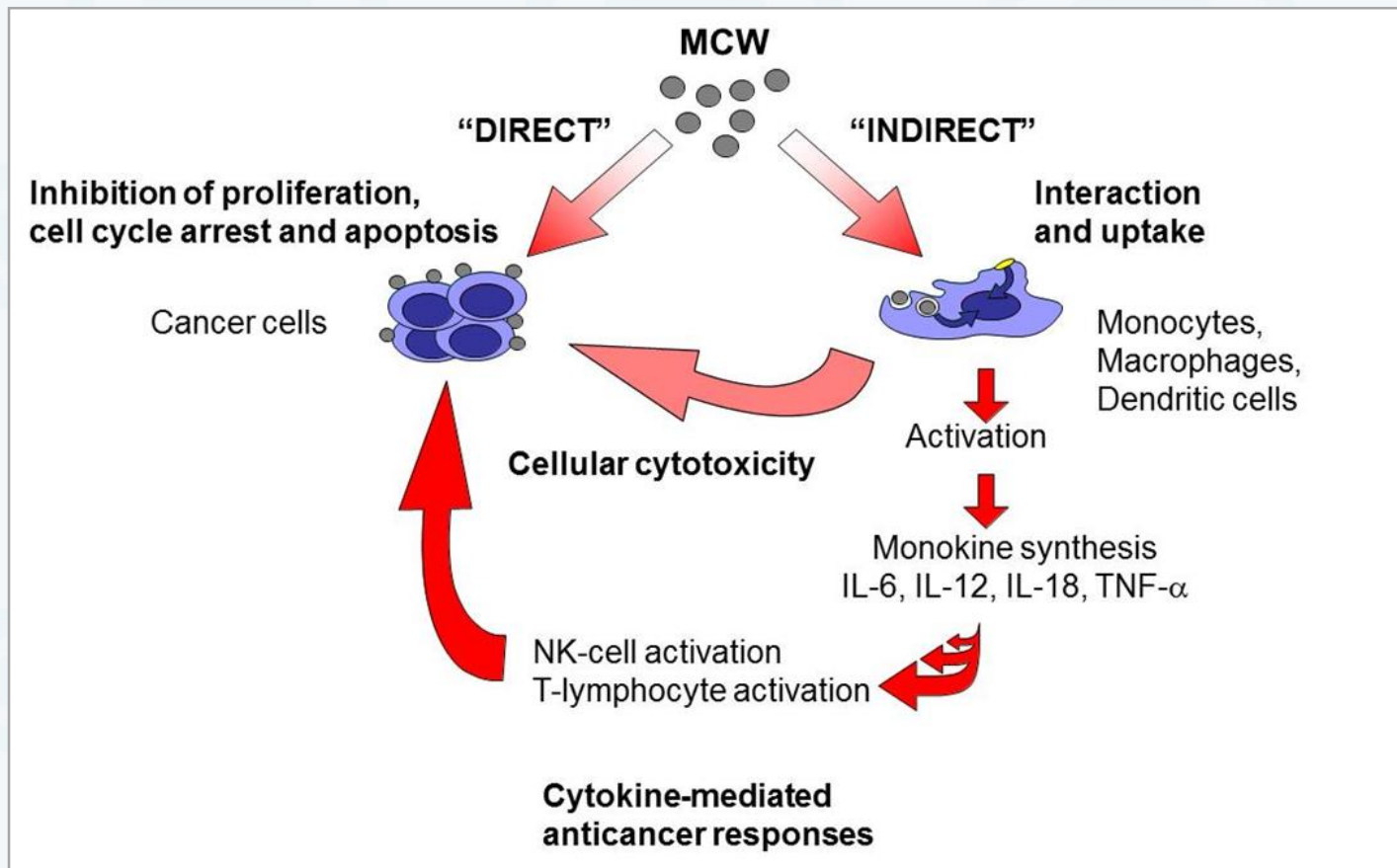
MCW-DNA Immune-Based Mechanism of Action

➤ MCW-DNA induces:

- ❖ Activation of immune system receptors (TLR-2, NOD-2)
- ❖ Cytokine production by immune system cells (monocytes, macrophages, dendritic cells)
- ❖ Colony stimulating factor production (G-CSF, GM-CSF etc.)
- ❖ In general, induction of innate immune responses and cell-mediated immunity.

MCW-DNA Immunomodulatory and Anti-Cancer Activity

- MCW-DNA exhibits immunomodulatory and anti-cancer activity by two mechanisms:
 - ❖ Indirect: via the induction of anti-cancer cytokines
 - ❖ Direct: limitation of cancer cell division by induction of apoptosis



Summary of results:

**Amelioration of chemotherapy
induced neutropenia**

Proof of Concept Study in healthy dogs

Objectives of the study:

- To induce neutropenia grade 3 & 4 in healthy dogs by IV administration of 3 mg/m² of chemotherapeutic agent vinblastine (VBL).
- To assess the ability of MCW-DNA (different doses) to ameliorate neutropenia induced by IV administration of 3 mg/m² vinblastine.

Experimental design

Table 1. - Experimental groups

Group	Number of animals	Vinblastine	MCW-DNA treatment
I	10	3 mg/m ² IV	NONE
II	10	3 mg/m ² IV	50 µg/kg
III	10	3 mg/m ² IV	100 µg/kg
IV	10	3 mg/m ² IV	200 µg/kg
V	10	3 mg/m ² IV	500 µg/kg

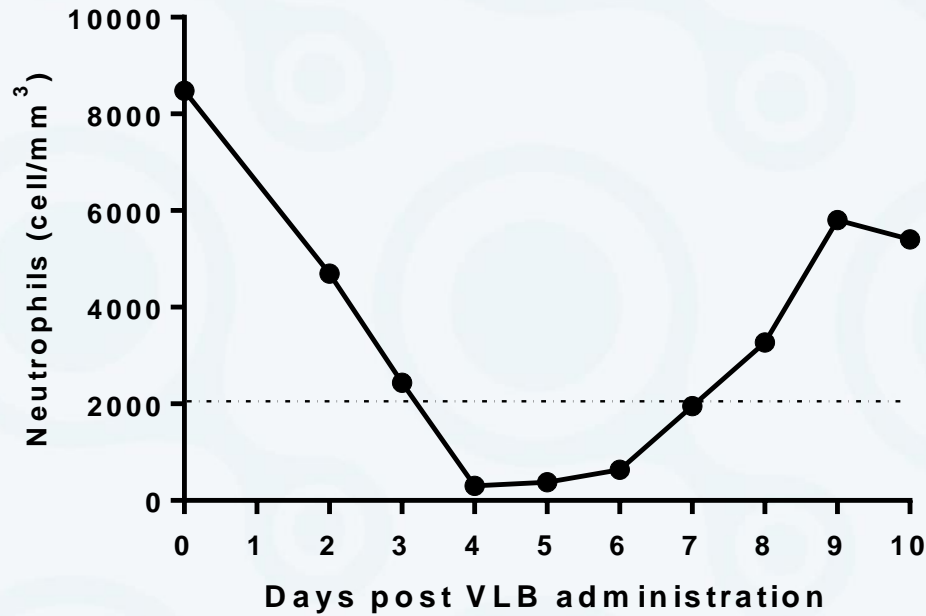
➤ Baseline for neutropenia based on: Neutrophils (<2000 cells/mm³)

Experimental design

	Day -7 to 0	Day 0	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Acclimatization minimum 7 days	X										
Health assessment	X										
BUN, SC, sAP, sALT	X										
CBC	X	X	X	X	X	X	X	X	X	X	X
Vinblastine treatment		X									
Neutropenia detected				X							
Allocation to treatment group				✕							
MCW-DNA treatment					✦						
Safety observations -adverse reactions					X						

- ✦ Mycobacterial Cell Wall-DNA (MCw_DNA) treatment is administered on one occasion only, 24 hours after neutropenia is detected. This occurs anytime from Day 2 to Day 7.
- ✕- Dog is allocated to treatment group at time of recruitment into study ie day neutropenia detected ($< 2,000$ cells/ μ L)
 - Animals were acclimated for 7 to 8 days
 - Blood samples were taken at the point of admission, on Day 0 and each following day until neutropenia is present or study completion (Day 10).
 - MCW-DNA was administered 24h after neutropenia was diagnosed.

Group I (Control)

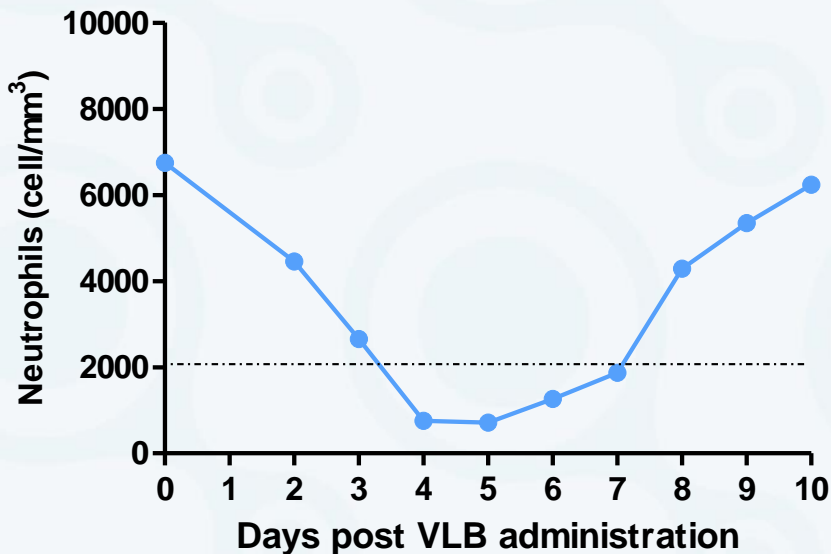


Median values

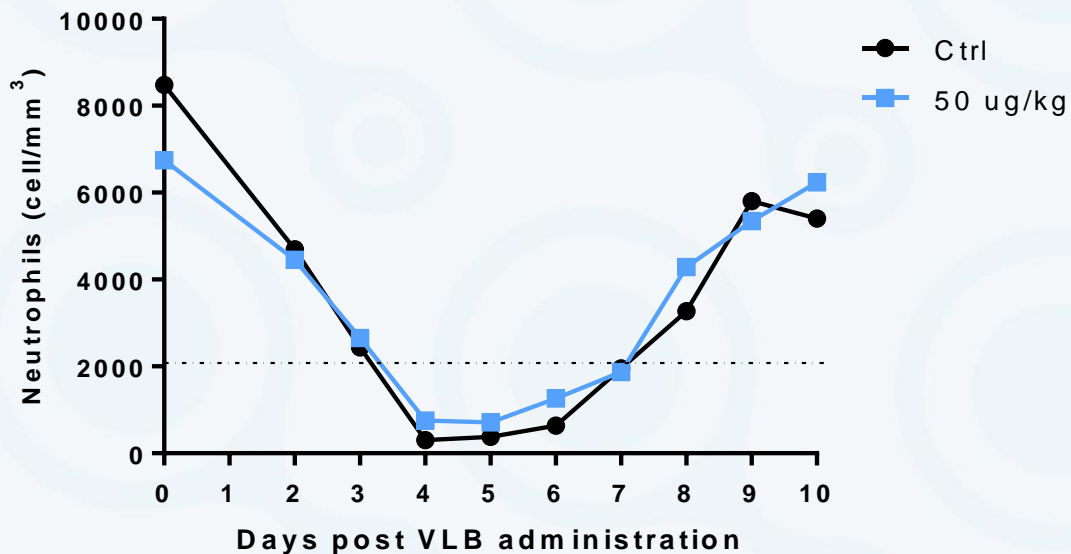
Weight (kg)	Dose Vinblastine (mg)	Start Day	Grade	Recovery Day	Recovery Period
16.5	2	4	4	8	4

* Recovery period (median): **4 days!**

Group II (50ug/kg)



Group I (Control) vs Group II (50ug/kg)



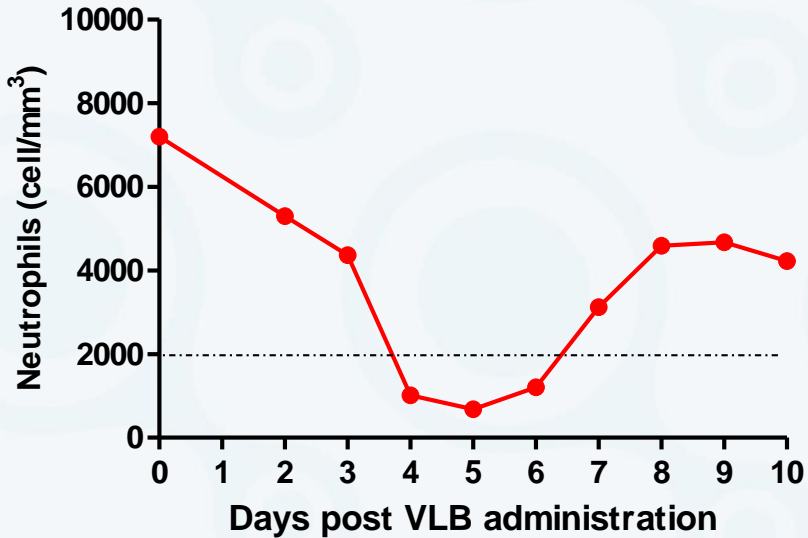
Not significant

Median values

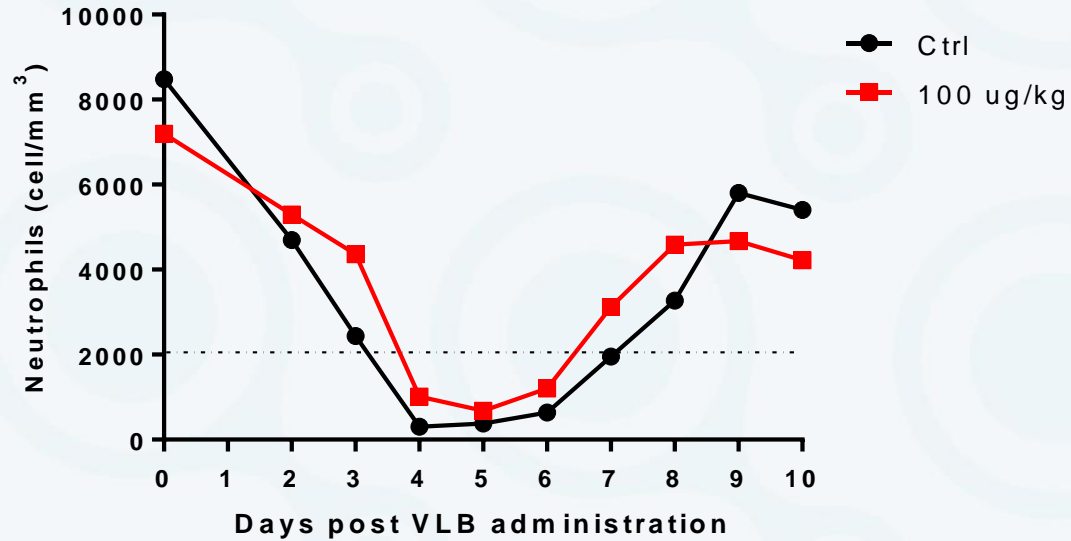
Weight (kg)	Dose Vinblastine (mg)	Dose MCW-DNA (mg)	Treatment Day with MCW-DNA	Start Day	Grade	Recovery Day	Recovery Period
14	1.8	0.7	4.5	4	3	7.5	3

* Recovery period (median) : **3 Days!**

Group III (100ug/kg)



Group I (Control) vs Group III (100ug/kg)



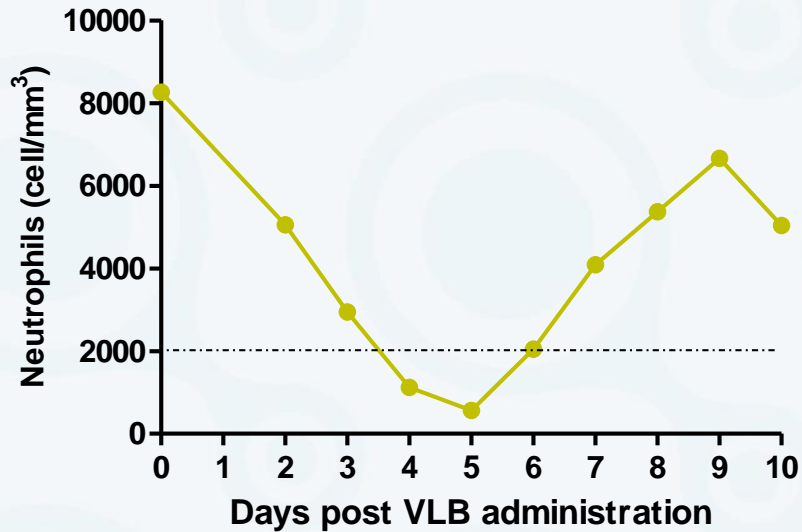
p<0.05 ; *significant

Median values

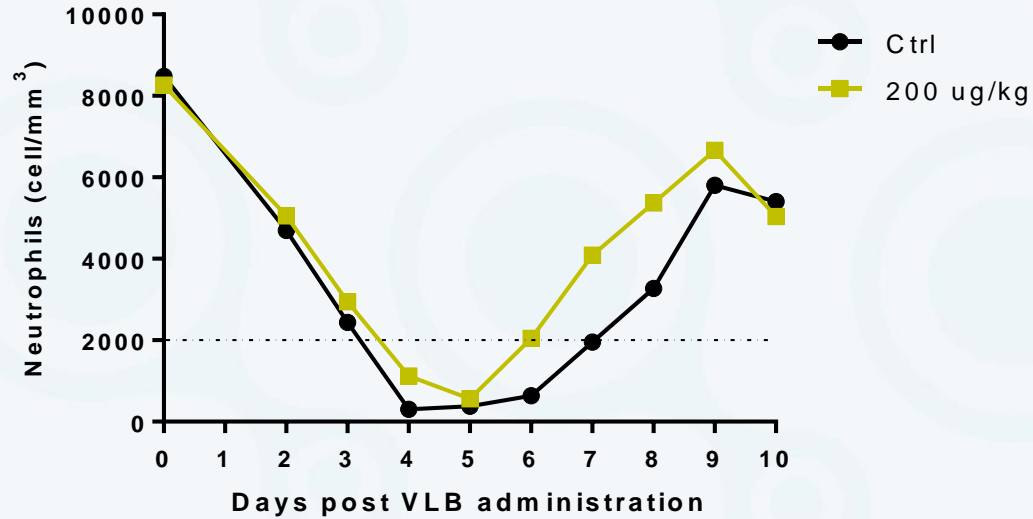
Weight (kg)	Dose Vinblastine (mg)	Dose MCW-DNA (mg)	Treatment Day with MCW-DNA	Start Day	Grade	Recovery Day	Recovery Period
14	1.7	1.4	5	4	3.5	7	2

* Recovery period (median): **2 days!**

Group IV (200ug/kg)



Group I (Control) vs Group IV (200ug/kg)



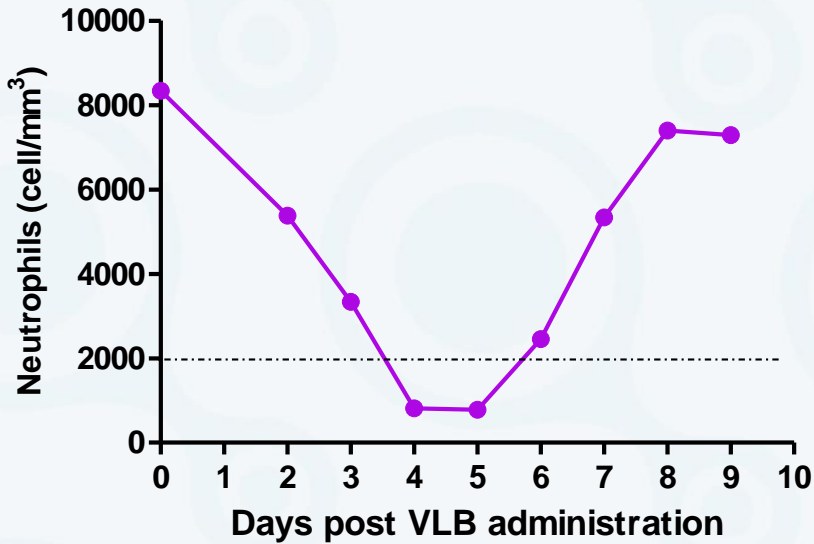
p<0.01; ** significant

Median values

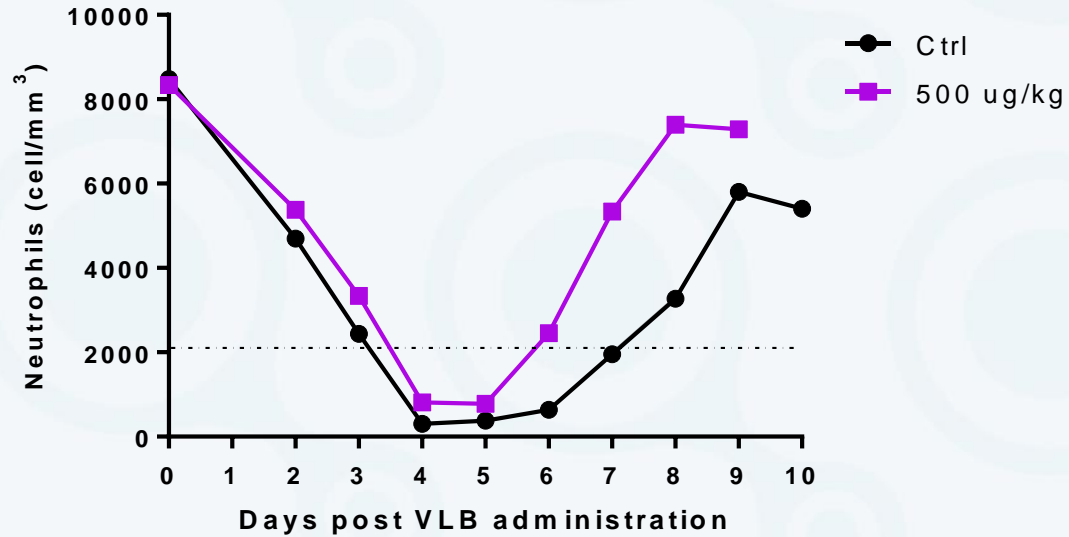
Weight (kg)	Dose Vinblastine (mg)	Dose MCW-DNA (mg)	Treatment Day with MCW-DNA	Start Day	Grade	Recovery Day	Recovery Period
13	1.7	2.65	5	4	3	6	2

* Recovery period (median): **2 Days!**

Group V (500ug/kg)



Group I (Control) vs Group V (500 ug/kg)

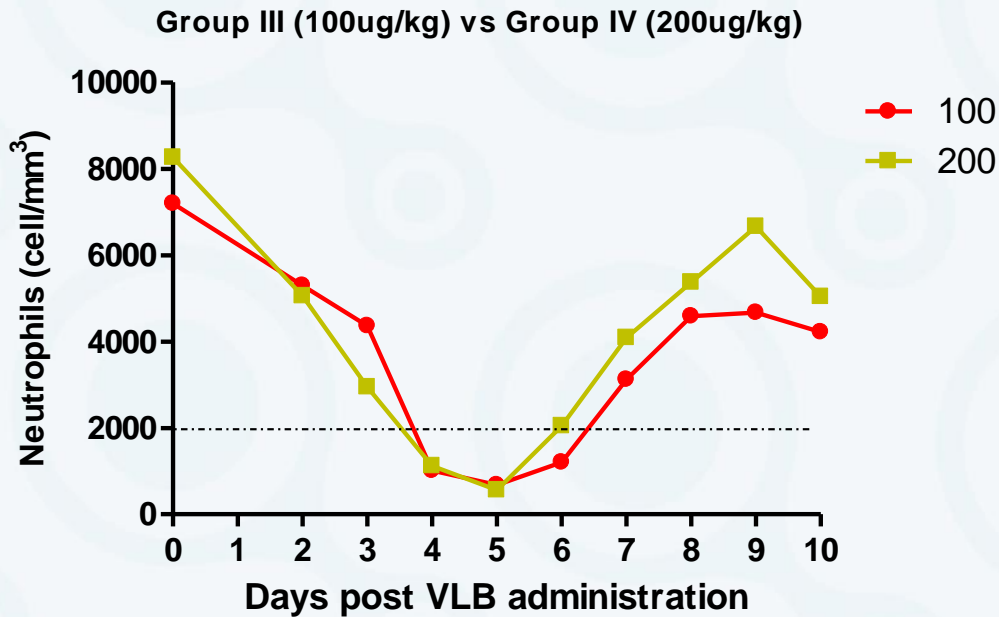


$p < 0.0001$; *** significant

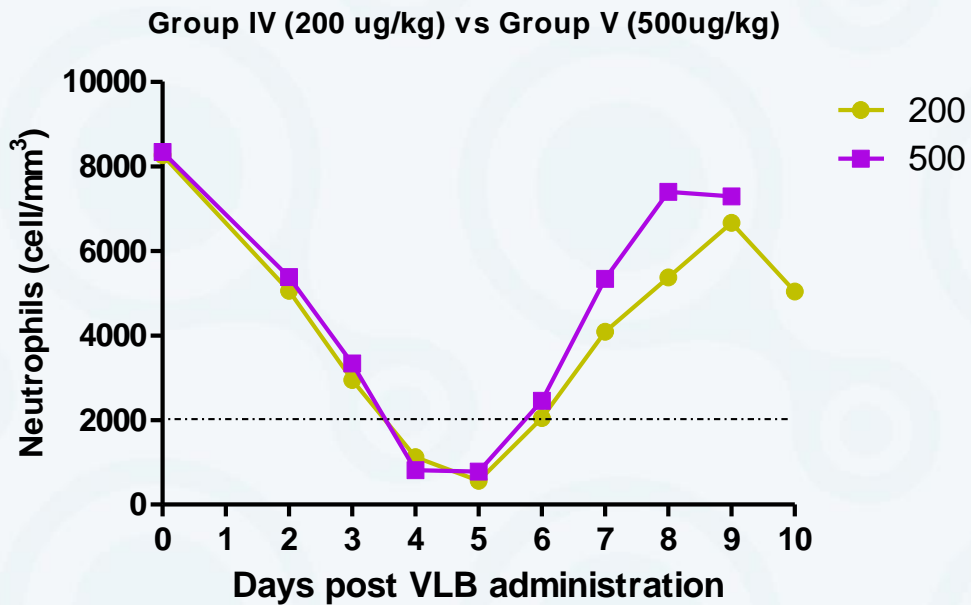
Median values

Weight (kg)	Dose Vinblastine (mg)	Dose MCW-DNA (mg)	Treatment Day with MCW-DNA	Start Day	Grade	Recovery Day	Recovery Period
13	1.65	6.5	5	4	4	6	1

* Recovery period (median): **1 Day!**

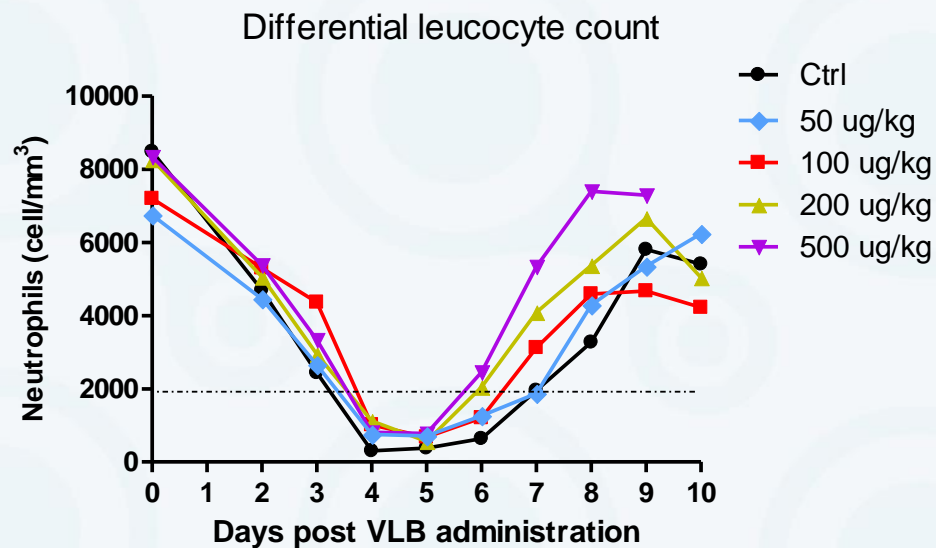


p<0.05; * significant



p<0.05; * significant

Summary:



Recovery time in days (median)

Group	Neutropenia
I (Control)	4
II (50 μ g/kg)	3
III (100 μ g/kg)	2
IV (200 μ g/kg)	2
V (500 μ g/kg)	1

Summary of results:

	Grade 1	Grade 2	Grade 3	Grade 4
Number of animals with neutropenia after VBL	0/50	5/50	19/50	26/50
% of animals with neutropenia after VBL	0%	10%	38%	52%

Group	Median neutropenia grade	Mean neutropenia grade
I (Control)	4	3.7
II (50µg/kg)	3	3.3
III (100µg/kg)	3.5	3.3
IV (200µg/kg)	3	3.2
V (500µg/kg)	4	3.6

Adverse reactions related to MCW-DNA administration (immediately after administration)

Five out of ten (50%) animals in group V (500µg/kg), two out of ten (20%) animals in group IV (200 µg/kg) and one out of ten (10%) animals in group III (100 µg/kg) showed some adverse reactions immediately following MCW-DNA administration:

Table 1. MCW-DNA related adverse events observed in dogs within each experimental group

Animal #	Group I (Control)	Group II (50ug/kg)	Group III (100ug/kg)	Group IV (200ug/kg)	Group V (500ug/kg)
1.	None	None	None	None	None
2.	None	None	None	None	None
3.	None	None	None	None	None
4.	None	None	None	None	H*
5.	None	None	None	None	T,*
6.	None	None	None	None	WG,T,H*
7.	None	None	None	WG, T,H*	D*
8.	None	None	D, WG*	None	WG*
9.	None	None	None	D*	None
10.	None	None	None	None	None

*WG-wobbly gait, D-dizziness, H-hyperthermia, T-tremor

Future directions

- MCW-DNA as an aid in the prevention and treatment of neutropenia following concurrent administration.
- MCW-DNA as an aid in the prevention and treatment of neutropenia following concurrent administration in tumor-bearing dogs !

Thank you!

Questions?



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