Chemotherapy in General Practice. Is it still possible??

RACHEL VENABLE, DVM, MS, DACVIM (ONCOLOGY)
HESKA CONSULTANT
AUGUST 3RD, 2023

PET CANCER CARE CONSULTING

HESKA

1

Points to Discuss

- What is chemotherapy
- What are the risks of handling
- Regulations
- Chemotherapy to give in the clinic

2

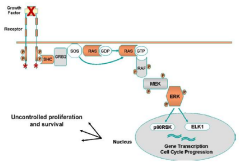
Chemotherapy

- What is chemotherapy?
  - Treatment of illness by chemical means
  - Anti-neoplastic therapy
    - Regimen of treatment aimed at destruction of malignant cells and utilizing a variety of chemical agents that directly affect cellular growth and development
      - *Saunders Comprehensive Veterinary Dictionary, Second Edition*

3

Chemotherapy

- Examples of chemotherapy
  - Maximum tolerated dose
    - Cause cells to die during cell cycle
      - Doxorubicin, carboplatin, vincristine, etc
  - Small molecule inhibitors
    - Targeted therapy
      - Palladia
      - Laverdia



4

Why Treat Chemotherapy Administration Differently?

- Increased risk of spontaneous abortion, malformations, low birth weight and congenital abnormalities in pharmacy and healthcare workers
  - 14 different studies since 1985
- Increased risk of infertility in males and females
  - *Dranitsaris, et al. J Oncol Pharm Pract 2005.*
- Increased risk of developing secondary malignancy
  - Increased DNA mutations and cancers
    - Multiple studies since 1970

5

Environmental Exposure

- Preparation and administration
- Contamination on bottles when delivered
- Accidental ingestion of contaminated food stuff; Hand-to-oral contact
- Treated pets-Urine and feces
- Multiple studies have found chemotherapy drugs in the urine of health care workers both directly and indirectly involved with the drugs

6

Exposure

Table 3
Persons at risk of exposure to chemotherapy

Persons at Risk	Phase of Process	Route of Exposure
Inventory personnel	Shipment receipt	Contaminated and/or leaking vials
All staff/personnel	Storage	Cross-contamination of vials and environment
All staff/personnel	Preparation	Spills, inhalation, dermal, and environment
All staff/personnel	Administration	Spills, inhalation, dermal, and environment
All staff/personnel	Patient care	Patient, contaminated housing, and patient excreta
All staff/personnel	Cleaning/waste disposal	Contaminated prep/administration areas/ materials, housing area/materials, patient excreta
Pet owners/family	Patient at home	Patient, patient excreta, oral anticancer agent storage/prep/administration

Klahn, *S Vet Clinic Small Animal*, 2014

7

Exposure

- Levels of exposure to chemotherapy 15x higher in veterinary medicine than human
  - *Meijster, et al. Ann Occup Hyg 2006*

8

Why Don't We Protect Ourselves?

- Not just veterinary
- Knowledge level not a factor
- Perceived susceptibility and severity of health problem
- Barriers
  - Inconvenience, discomfort, cost, and time
- No recommended exposure limits
  - Unlike radiation

9

Legislation

- Hazardous drugs
- OSHA and USP
  - OSHA regulations include USP <800>
  - Now includes veterinarians and veterinary technicians
  - https://www.osha.gov/SLTC/hazardousdrugs/controlling_occex_hazardousdrugs.html#work_area
- NIOSH guidelines voluntary
  - 2016 updated Hazardous Drug Handling in the Healthcare Setting
  - http://www.cdc.gov/niosh/docs/2004-165/
- Legally and ethically obligated to educate staff on safe handling

10

How to Protect Ourselves

- Eliminate the hazard
- Engineering controls
  - Now required by OSHA
- Administrative controls
  - Now required by OSHA
- Personal Protective Equipment (PPE)
  - Now required by OSHA

11

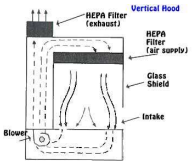
How to Protect Ourselves

- Eliminate the hazard
  - Best way to protect self and staff
  - Do not administer
  - Refer to practice equipped to handle and administer chemotherapy

12

Engineering

- Vertical laminar flow hoods (Biological Safety Cabinets (BSCs))
  - Protect worker from aerosolization and containment of spills when preparing chemotherapy drugs
  - Study showed nurses lacking VLFH had higher frequency of chromosomal aberrations. But all groups of nurses had higher levels than controls so VLFH is not enough in itself
    - *Jakab, et al. J Toxicol Environ Health 2001*



13

Engineering

- OSHA requires Containment Primary Engineering Control (C-PEC)
  - Biological Safety Cabinet (BSC) Class II, type A2, B1 or B2
  - Facility managing hazardous drugs must have designated C-PEC or sending patient to facility with C-PEC
  - External ventilation
  - C-PEC must be located in Containment Secondary Engineering Control (C-SEC)-i.e. own room separate from rest of facility
- C-SEC
  - Negative pressure in room
  - Externally ventilated
  - Sink and plumbing specific for room
  - Sterile procedure in room

14

Administration

- Warning signs
- Training
  - Test every 12 months
- Operating procedures
- Buddy system
- Closed system transfer devices

15

Administration

- Closed system chemotherapy
  - Needless devices approved by the FDA
    - Ex. PhaSeal, Tevadaper, ChemoClave, and Equashield, etc.
  - Decreased surface contamination
  - Prevent aerosol exposure and no sharps
  - Still need to have BSC
  - NIOSH recommends and OSHA with USP mandates when applicable-i.e.(IV chemotherapy)

16

Equashield



17

The PhaSeal® System




18

Personal Protective Equipment

- NIOSH, OSHA, and USP
  - Require PPE when handling and administering chemotherapy
  - Double gloves
  - Gowns
  - Hair and shoe covers
  - +/- Face shields

19

Acute Exposure

- Skin irritation, sore throat, cough, dizziness, headache, allergic reaction, diarrhea, nausea, and vomiting
- Seek medical attention
- Spills kits on site
- Trained staff

20

Disposal

- Chemotherapy waste containers
  - Different than red sharp containers
  - Gloves, gowns, chemotherapy administration set, chemotherapy
    - Put in small bag first and seal then place in larger container
  - NIOSH, OSHA, and USP require specific disposal containers

21

22

How is Oral Different?

- Not included in all USP 800 or USP 795
- Only need gloves
- Exposure
  - Handling pills
  - Touching containers
- Do NOT split tablets or open capsules

23

Oral Chemotherapy

- Small molecule inhibitors
  - Palladia (toceranib), Laverdia
- Chemotherapy
  - Cyclophosphamide, chlorambucil, lomustine, melphalan, procarbazine, methotrexate, and hydroxyurea
- Metronomic chemotherapy

24

Oral Chemotherapy Safe Handling for Owners

Dos	Don'ts
Review label for dosing	Store medications with other medications, near food, or where accessible by children
Wear gloves when unpacking shipments from compounding or mail order pharmacies	Assume oral chemo is safer than IV
Store medication under conditions as directed	Crush, split, or allow pet to chew tablets
Wear gloves when administering medication, wash hands before and after	Open capsules
Report overdosing immediately	Skip or double doses unless instructed by vet
Minimize the # of people in contact with medication	Modify or alter dose of schedule without consulting vet
Wear gloves when handling excreta	
Wash bedding separately	
Return unused or damage drug to vet for disposal	

Adapted from Goodin, et al. Safe handling of oral chemotherapeutic agents in clinical practice: Recommendations From an international pharmacy panel. J Oncol Pract 2011.

25

Palladia (toceranib)

- TKI
  - Receptors
    - VEGFR, PDGFR, Kit
  - Antiangiogenic and direct antitumor activity

Liao, Blood, 2002
Pryer, Clinical Cancer Research, 2003

petconnection.com

26

Palladia Toxicity

- Toxicity
  - GI
    - Grade 3-4 vomiting, diarrhea, anorexia
  - Musculoskeletal
    - 17% Grade 1-2 lameness
  - Hematology
    - 24% elevated ALT
    - 46% neutropenia and 24% thrombocytopenia
      - All low grade

"Eat some grass, and call me in the morning."

27

Palladia Toxicity

- Toxicity
  - Hypertension (SBP >160 mmHg)
  - Protein losing nephropathy

Tjostheim SS et al. JVIM 2016

28

Palladia: 28 different studies other than MCT (retrospective, prospective, case reports)

- GIST
- Anal sac adenocarcinomas
- Metastatic osteosarcoma
- Heart based/chemodectoma
- Insulinoma
- Pheochromocytoma
- Thyroid carcinoma
- Lymphoma
- Renal cell carcinoma
- Adenocarcinoma

Frezoulis P, VCO 2022

29

Imatinib (Gleevec)

- Used more in humans
- Commonly compounded in veterinary medicine
- Study found 48% of dogs with gross mast cell disease responded
- KIT mutation did not affect response

30

Laverdia (verdinexor, KPT-335)

- SINE (Selective Inhibitors of Nuclear Export)
- Exportin-1 (XP01)

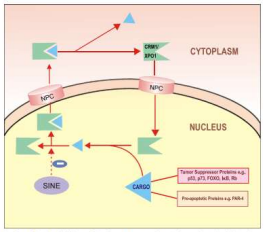


Figure 1 Mechanism of action for selective inhibitors of nuclear transportation. In the nucleus, RanGTP and cargo (tumor suppressors, pro-apoptotic proteins, etc.) form a complex with CRM1/XPO1. This complex is exported through the nuclear pore complex (NPC) to the cytoplasm. CRM1 is then recycled back to the nucleus for another round of export. Selective inhibitors of nuclear export (SINE) binds to CRM1/XPO1 and blocks the protein export, and therefore the cargo proteins are retained in the nucleus, leading to growth inhibition.

Parikh, J Hematol Onco 2014

31

Laverdia (verdinexor)

- Oral selective inhibitor of nuclear export (SINE) KPT-335
- Phase II study dogs with LSA, 58 dogs (naive or progressive).
  - ORR 37% (T cell ORR 71%), TTP 29 days (range: 7-244 days)
  - Dogs on steroids with drug TTP 73 days

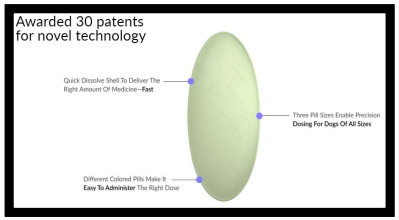
Sadowski et al. BMC Vet Research, 2018

https://anivive.com/laverdia

32

Laverdia Toxicity

- Side effects
  - Grade 1-2 GI
  - 3 dogs had serious AE including weight loss, weakness, hepatopathy, one dog developed PLN
- Does not cause drug resistance like prednisone



33

Lomustine (CCNU, 1-(2-chloroethyl)3-cyclohexyl-1-nitrosurea)

- Alkylating
  - Bind alkyl groups to DNA bases
  - Leads to breaks in DNA causing cytotoxicity

34

Lomustine Toxicity

- Hepatotoxicity
  - Denamarin study
- Significant neutropenia

Hosoya, VCO, 2009
Skorupski, J Vet Intern Med, 2011
Heading, Aust Vet J, 2011
Skorupski, J Vet Intern Med, 2011

35

Lomustine Uses

- Mast cell tumors
- Epitheliotropic lymphoma
- T cell lymphoma
- Feline GI large cell lymphoma
- Histiocytic sarcoma
- Brain tumors

36

Cyclophosphamide

- Alkylating agent
  - Bind alkyl groups to DNA bases
  - Leads to breaks in DNA causing cytotoxicity
- Reduce Treg and MVD

37

Cyclophosphamide Toxicity

- Cyclophosphamide induced Sterile Hemorrhagic Cystitis
  - 9% develop SHC without Lasix vs. 1.2% that received Lasix
  - Total dose divided over 3 days and no dog developed SHC
  - Metronomic cyclophosphamide
    - 30% developed SHC not on Lasix vs 10% on Lasix
  - Substitute chlorambucil for cyclophosphamide

Setyo, VCO 2015, Chan, JAVMA 2016, Harper, JSAP 2017

38

Cyclophosphamide Uses

- Lymphoma (part of protocols)
- Leukemia
- Sarcoma (metronomic chemotherapy)
- Mast cell tumors
- Mammary carcinomas
- Resistant multiple myeloma
- Immune mediated diseases

39

Chlorambucil

- Alkylating agent
  - Bind alkyl groups to DNA bases
  - Leads to breaks in DNA causing cytotoxicity

40

Chlorambucil Toxicity

- Myelosuppression (rare, but can see more with chronic use)
- Nausea
- Neurologic (rare, more in cats)
- Pulmonary fibrosis (very rare)

41

Chlorambucil Uses

- Low grade, small cell lymphoma
  - Indolent, T zone
  - Small cell intestinal lymphoma
- Chronic lymphocytic leukemia
- Urothelial carcinoma (UC) or Transitional Cell Carcinoma (TCC)
- Mast cell tumors
- Resistant multiple myeloma
- Substitute for cyclophosphamide
- Immune mediated diseases
- Lots of metronomic chemotherapy

42

Metronomic Chemotherapy (MC)

- Uses traditional chemotherapy drugs
- Low dose-Less toxic
- Continuous-No breaks
  - Decreasing time for tumor cells to grow
- Targets tumor endothelial cells
- Rare chance of developing acquired drug resistance

43

How Does It Work?

- Inhibits angiogenesis and vasculogenesis
- Modulates the immune system
- Decreases Treg and impairs function
- Direct anti-tumor effects
- Increases apoptosis
- Disrupt cancer stem cells (CSC)
- Tumor dormancy

44

When to Use It?

- Published trials
- Significant metastatic disease
  - MTD chemotherapy may produce too much SE
- Tumor cannot be treated with surgery or RT
  - Or declined by owner
- Traditional chemotherapy unlikely to help
- Primary tumor has been removed but chance of regrowth or spread is high
- Maintenance therapy?

45

Drugs for MC

- Chemotherapy (see earlier slides)
  - Cyclophosphamide, Chlorambucil, CCNU
- Piroxicam-NSAID
  - Non specific COX-1 and COX-2 inhibitor
  - Anti-angiogenic
  - Anti-inflammatory

46

Dosage for MC

- Wide range of dosages reported
- Best dose and schedule unclear
- Do not always fit commercially available size
- Careful compounding chemotherapy
  - Variability in dosage and quality
- AVMA compounding policy
  - https://www.avma.org/KB/Policies/Pages/Compounding.aspx

47

Compounding

- Compared CCNU from 5 compounding pharmacies
  - Potency ranged from 50-115% of labeled concentration
- Cyclophosphamide from 5 compounding pharmacies
  - Analyzed potency at 2 time points: 4/10 samples were inadequate
  - Stability at 60 days was acceptable in all but 1 sample

Burton, JVIM 2016, Robat, VCO 2017

48

Monitoring

- Recheck exams and blood work 2 weeks then every 4-8 weeks
- Urinalysis if on cyclophosphamide
- Typical RECIST criteria may not be best for MC
  - Goal QOL and long-term therapy

49

Sum It Up

- Handle chemotherapy drugs carefully
- Understand safety and regulations (especially IV chemotherapy)
- Can dispense chemotherapy pills without extra equipment or regulations
- Owner education

50

Questions?

Remember to **download the CE certificate** in the handouts panel of the webinar control panel.
NOTE: CE certificate not available for watching the recording.

Questions about CE?
events@heska.com

Questions about topic?
venable@petcancercareconsulting.com

Thank you for joining us!

HESKA

PET CANCER CARE CONSULTING
www.PetCancerCareConsulting.com

51