Lymphoma: ANYTHING NEW?

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VCA SPECIALTY ANIMAL HOSPITALS

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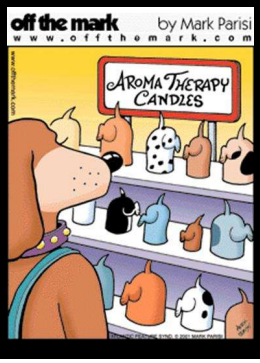
Lymphoma Update

- Areas we'll review:
  - Brief Overview:
    - History
    - Workup
    - Diagnosis
    - Prognosis
  - Chemotherapy Protocols
  - Rescue Protocols
  - The Future?



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Lymphoma Review

- Most common hematopoietic tumor (>90%)
  - 2nd most common tumor in dog (MCT)
- LN or visceral involvement most common
- Generalized lymphadenopathy RARE in cats
  - Always BIOPSY these cases, WHY ?
- Breed predilection
  - Dogs: Goldens, Scotties, Boxers, Bassetts, Bulldogs
    - Rottweilers
      - Jagielski et al, J Vet Med A Physiol Pathol Oct 02
    - Boxer & dog de Bordeaux at risk for T cell LSA
      - Jankowska et al, VCO 2015 & ActaVetHung 2019
    - EU = Dobie, Rottie & Bernese Mtn Dog – NOT Golden!
      - Comazzi & Teske et al, BMC Vet Res 2018

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Lymphoma Review

- Canine Anatomic Distribution:
  - Multicentric - 80%
  - Mediastinal - 5%
  - Alimentary - 5-7%
  - Miscellaneous 8-10%
    - Renal, Neuro, Nasal, Skin, Eye, etc

Various studies, 1970 - Present

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Lymphoma Update

- Etiology
  - Presently UNKNOWN
  - Retrovirus suspected but not proven
  - Cyclosporine-based Immunosuppression
    - Renal transplant cats; Schmiedt et al UW, VCO '09
    - 6.7X risk of LSA vs control cats (Wormser et al, VCO '14)
  - Association with spay/neuter?
    - Early PILOT data suggests MAYBE
      - ~ 3-5X increased risk BUT < 10-15 cases – TRUSTABLE?
      - Torres de la Riva et al, PLOS one 2013
    - BETTER data suggests risk is MUCH LESS
      - Risk is ~ 25-30% more in spayed females
        - Villamil et al, JCancerEpidem 2009
      - True across multiple species

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Lymphoma Update

- Etiology – cont'd
  - Association with toxins?
    - Phenoxyacetic acid herbicides (humans)
    - Herbicide lawn treatments and dogs (controversial)
      - What canine tumor is this associated with??
    - Residence in industrial area (Gavazza et al, JVIM May 01)
    - Secondary smoke in cats (Bertone et al, Aug 02)
    - Use of paints & solvents (Gavazza et al, JVIM May 01)
  - Association with Bartonella?
    - Bartonella (blood and LN) equal in LSA vs Normal Golden's
      - Doesn't disprove causation; longitudinal studies needed
      - Duncan & Breitschwerdt et al, JVIM 2008

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Clinical Presentation

- Multicentric/Mediastinal/Alimentary
  - ADR, lethargy, anorexia, wt loss, V/D
  - Greatest chance of paraneoplastic hypercalcemia??
- Renal
  - Renal failure, pain, above
- Spinal/CNS
  - Posterior paresis, signs of pain, ataxia
- Other sites typically have signs specific to area involved (eg nasal, skin, eye)
- *Lymphoma does what lymphoma wants*

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Staging & Diagnosis

- Minimum needs:
  - Complete PE
  - CBC, Biochem Profile, UA
  - Aspirate/Biopsy of abnormal tissue/fluid
    - Biopsy if which peripheral node??
- Other possible diagnostics
  - Radiographs (chest, abdomen, other)
  - Bone marrow aspirate
    - Is a normal CBC = no need to do marrow?
      - NO! Martini et al, Vet Comp Oncol 2013
  - Ultrasound and aspirate/biopsy or exploratory
  - NEW – New River VDL "LymphoPro"
    - Feline IBD vs LSA on histo
    - CAUTIOUSLY optimistic – small validation study

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Staging & Diagnosis

- Staging via aforementioned diagnostics
- Why is staging preferred when possible??
  - Prognostic
  - May guide Rx decisions
    - How may it guide Rx decisions??
  - May influence willingness to treat
- Difference between stage and grade ??
- What is stage migration?
  - More sensitive tests over time = greater stage

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Is cytology good enough??

- Depends on the species and anatomic site
- Canine
  - Can be diagnostic for large cell LSA
    - Small cell LSA Dx on cyto = essentially impossible
    - Don't trust mandibular LN cyto Dx of LSA (drains oral cavity)
  - Grade is prognostic; Bx WHENEVER POSSIBLE
    - Especially cases of "Lymphoid hyperplasia vs LSA"
  - SOME Indolent LSA's = no therapy
    - Valli et al, Vet Pathol 2006; Seelig & Avery et al, JVIM 2014
- Feline
  - BE CAREFUL!!
    - I trust kidney as a site for cyto-based LSA Dx; Why??
    - All other sites relate to cyto read & trust of cytologist
  - FALSE POSITVES & NEGATIVES HIGH (30-90%)
    - Ku et al, VCO 2016 (Esp mesenteric LN Cyto's)

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LSA Staging

Stage I	Single tumor or anatomic site
Stage II	Single tumor with regional nodes +
	2 tumors/nodes 1 side of diaphrm
	GI tract tumor indep of nodes
Stage III	Disease on both sides of diaphrm
	Unresectable abd tumor/spinal dz
Stage IV	I, II or III with liver or spleen
Stage V	I - IV with marrow or CNS +

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Chemotherapy for LSA

- Most protocols derived from human LSA
- Multiagent protocols *generally* better
  - Increases cost & complexity
  - May increase toxicity
  - Adria containing multiagent protocols like CHOP best
    - Hosoya et al, JVIM 2007 & Rassnick et al, JVIM 2007
  - Significant increases in rem/surv time not realized to date in cats (opposite of canine)
- FIRST remission is generally longest one
- Pred NOT beneficial in multi-drug protocols
  - Zandvliet M et al, VetJ 2013
  - Childress et al, JAVMA 2016
- Outcomes discussed are for "average" stage II-IV

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Chemotherapy for LSA

- No Treatment
  - Median survival = ~ 30 days
- Prednisone alone
  - Dogs: 1/3 CR, 1/3 PR, 1/3 NR
  - Median remission = 30-45 days
  - Median survival = ~ 60 days
    - "How could it be so short doc, my dog is so healthy??"

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Chemotherapy for LSA

- COP protocol (cytoxan, vincristine, pred)
  - Dogs: 60% CR, median rem = 130-150 d
  - Cats: 47% CR, median rem = 62-83 d
  - IP COP? Teske et al, Vet Comp Oncol 2012
    - 77% CR for ~ 400d – VERY WELL TOLERATED!
    - High percentage of nasal LSA
  - EQUAL PK/PD with IV vs PO
    - Warry & Lana et al, JVIM 2011; Stroda et al, AJVR 2017
  - Vinc GI Tox? OK to switch to vinblastine!!
    - Krick et al, JVIM 2013


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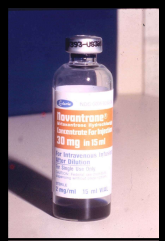
Chemotherapy for LSA

- Idarubicin
  - Oral doxorubicin derivative
    - Median remission time = 183 days (cats)
      - Moore et al, '97
- Mitoxantrone
  - Poor induction agent
    - Maintenance agent?
    - Dose = 6.5 mg/m^2 (cats)
      - 5.5-6.0 mg/m2 (dogs)
      - Ogilvie et al



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Chemotherapy for LSA

- Adriamycin (doxorubicin)
  - DOGS: 62% CR, median rem = ~150-170 d
  - CATS: 32% CR, 32% PR, 36% NR
    - Doxorubicin alone not routinely recommended
      - Peaston et al, Aust Vet J 99
      - Kristal et al, JVIM Mar 01
    - Use doxorubicin in concert with other LSA agents
    - Std of care = 1 mg/kg in cats
      - Hepatic & Renal toxicity when used at 30 mg/m^2
      - Tolerated extremely well in most cats (too well?)
      - Is 1 mg/kg too low a dose?
      - My dose for cats = 25 mg/m2
        - Reiman et al, J Fel Med Surg 2008

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Chemotherapy for Canine LSA

Therapy	Remission %	Median Rem (mos)	Median Surv (mos)
None	0 %	0	1-2
Pred only	1/3	1	2
COP or A	~ 60%	4-6	6-8
A&C ('10)	~ 70%	8	?
CVT-X or CHOP	80-82%	5-7	8-11
UW-2yr	82%	8	11-12

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Chemotherapy for Canine LSA

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UW-2yr	82%	8	11-12
UW-25wk	92%	9.5	13

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Quality of Life on Chemo??

- Mellanby et al, JSAP '03
  - Dogs with LSA undergoing multi-agent chemo
  - 92% had no regrets and would treat again
  - 68% said QOL same on chemo as before dx
  - 32% said QOL worse on chemo, but still acceptable in all cases
- Tzannes et al, JFMS '08
  - Cats receiving COP; N = 31
  - QOL score = 1 – 10, 10 is best
  - Before chemo = 3.9 vs. On chemo = 6.3
  - 83% happy they treated, 87% would treat again
- Bottom line = QOL is good while on chemo!

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UW-25 week vs 2 years?

- Garrett LD et al, JVIM 02/Chun R et al, JVIM '00
  - 53 dogs with multicentric LSA
  - CHOP-based UW-25 week
    - Compared to historically-reported maintenance chemo protocol
  - 92.3% CR & 1.9% PR
  - Remission = 9.5 months & Survival = 13 months
    - No difference compared to similar protocol with maintenance
    - P > 0.28
  - ~ 40% required Rx delay or dose modification & 9% hosp rate
    - Generally during induction – esp. Week 1 Vinc/Elspar
    - Why is week 1 problematic?
  - What about UW-19?? 15?? 12??

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Elspar, Elspar, Elspar??

- Do we really need to use Elspar® for Lymphoma?
  - Randomly available, expensive & possible side effects
  - TWO studies say NO!
  - MacDonald et al (UW-Madison), JVIM 2005
    - 84 dogs CHOP-Elspar vs 31 dogs CHOP (UW-19 week)
    - No differences in remission, survival, or response rate
    - Median remission was ~ 7 mos for UW-19 (less than UW-25!)
    - "more appropriate to reserve for use in relapse"
  - Jeffreys et al (Purdue), JAAHA 2005
    - 42 dogs COP-Elspar vs 34 dogs COP
    - COPA remission = 6 mos vs COP remission = 3 mos
      - BUT not statistically different
- Elspar may be more useful in LESS dose intensive protocols like COP or possibly Adria alone
  - Big problem = lack of availability!

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Other therapies

- Radiation therapy
  - LSA is an extremely radiosensitive tumor
  - Generally used in concert with chemotherapy
    - Most commonly used for extra-nodal LSA
    - Recurrence of LSA outside of NASAL RT field common
      - Elmslie et al, Vet Radiol Ultras 1991
      - Meier et al, VetCompOncol 2019
    - May have use in Hodgkin's like LSA in cats
      - Staging is critical
      - Spread beyond local site = need for systemic therapy
  - Half-body RT??
    - Underwhelming to poor results to date
      - Williams et al, JVIM 2004; Gustafson et al, Vet Comp Oncol 2004
      - Rassnick et al, JVIM 2007; Vet Comp Oncol '08
    - Whole body needed but have to perfect technique

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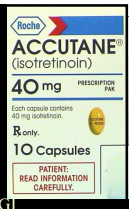
Other therapies



- Mycosis Fungoides
  - Epitheliotropic T-cell cutaneous LSA
    - Skin placques/erosions/ulcers
    - Recently reported case study & series in feline GI
  - Rx: Surgery and chemotherapy
  - NEW Rx: Accutane (isotretinoin)
    - 3-4 mg/kg per day
      - Can be hepatotoxic & KCS; teratogen
      - Dogs: ~ 50% CR for extremely variable length
        - Rosychuk et al, JAVMA (unknown efficacy in cats)
  - NEW Rx: CCNU (Lomustine)
    - 70-78% response rate (12-17% CR), median 106 days
      - Williams et al, JVIM 2006
      - Risbon et al, JAVMA 2006

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Other therapies

- When should I use Leukeran/Pred?
  - Leukeran = chlorambucil
    - "SLOW" alkylater
      - Takes long time to "ramp up"
      - Also takes a long time to get out of system!
  - Appears to be of use in:
    - Cats with high-grade IBD vs low-grade LSA
      - Other sites with small cell LSA in cats if multicentric
        - Kiselow et al, JAVMA 2008
          56% CR & 39% PR; MST = ~ 2 years
      - Not useful in larger cell LSA in cats
        - Fondacaro et al, Eur J Comp Gastroenterol 1999
    - Dogs with CLL (chronic lymphocytic leukemia)
    - Dogs with small cell LSA's
      - MST ~ 2 years – Couto & Skorupski et al, VCO 2018

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Atypical Lymphoma Sites

- Renal Lymphoma - CATS
  - Usually present for renal failure
  - Typically bilateral disease
  - Irregular, enlarged ± painful kidneys
  - Dx via aspirate/biopsy of kidney
    - AbdUS support = 100% Sens/Spec on cyto
      - McAloney et al, JFMS 2018
  - Rx with chemo with cytosar
    - 61% CR with median surv = 6 months
      - Mooney et al, JAVMA '89
    - Why cytosar?? Other drugs??

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LSA Rescue

- Difficult subject
  - Many options, but few work well
  - Best remission is the first
    - Do NOT wimp out on chemo
      - 5-10% dose reduction = 30-50% reduction in efficacy
      - Keep on protocol schedule!!
  - "Law of halves or less"
    - If 1st rem = 80% CR and 8 mos
    - Then 2nd rem generally = 40% CR and 4 mos
    - Then 3rd rem generally = 20% CR and 2 mos
  - Greater # agents for 1st remission
    - Somewhat lesser chance for subsequent rescue

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LSA Rescue Options

- Go back to original protocol?
  - Whenever previous remission outcome as expected or BETTER
- Tanovea (Rabacfosadine), VetDC
  - FDA Approved 2021
  - Highly active but toxicities = GI/Marrow/Pulmonary/Derm
  - 45% CR & 74% OR with PFI = 108d (203d for CR's)
  - Alternating Adria & Tanovea (3 each) = CHOP!!
- MOPP (Mustargen, vinc, procarb, pred)
  - ~ 60% SD/PR/CR
    - Rassnick et al, JVIM '02; Northrup et al, VCO '09
    - Back et al, VCO '13; Huss et al, JFMS '19
- CCNU (Lomustine) or LOPP/LPP
  - 26-50% PR/CR for median of 84-86 days
    - WATCH ALT's- Denamarin as hepatotoxic prevention
      - Skorupski et al, JVIM 2011
    - Compounded = less drug ☹
      - KuKanich et al, JAVMA 2017

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LSA Rescue (cont.)

- CCNU & DTIC
  - N = 57 dogs
  - 35% ORR; 23% CR & 12% PR; median remission 83 days
  - Neutropenia was DLT (nadir at d7)
    - Flory et al, JVIM 2007
  - Not much better than CCNU alone or DTIC alone – Don't use!
- Temozolomide or Dacarbazine & an Anthracycline
  - N = 63 dogs
  - 72% ORR; median remission 40-50 days
  - Dacarbazine caused significant hematologic toxicity
    - Dervisis et al, JAVMA Aug 2007
- "Others"
  - Elspar/Mitoxantrone, Vinblastine
  - DTIC/Adria, Platinum's, Doxil
  - DMAC, RT??, others

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Canine LSA Prognostic Factors

Strong	Medium	New
Substage	Stage	Prolif Mk
Grade	⇑⇑ Ca^{+}	P-Glyco
B vs. T	Gender	Pulmonary
Location	Weight	Steroid use
Response	⇓ albumin	Apoptotic

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Feline LSA Prognostic Factors

- What are the biggies?? (Vail et al, JVIM 1998)
  - Substage
  - FeLV status
  - Response to Therapy
- Medians for all cats?
  - 50% response with median remission 5-7 months
  - IMPACT of Sx then CHOP? Gouldin/Clifford et al, VCO '15
    - DFI = 12 months & MST = 14 months
  - WHY I recommend Sx and/or RT pre-chemo if possible
  - Ends of spectrum??
    - Substage b/FeLV+/No resp to chemo = weeks
    - Substage a/FeLV-/Good response = 9 months (25% > 2yr)
- Stage & Marrow Involvement
  - Brenn & Bergman et al, Vet Comp Oncol 2008

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Lymphoma

- Should I do chemosensitivity assays??
  - Human oncology
    - Generally not used & Minimally predictive
    - 2011 ASCO Roundtable = No assays currently recomm'd
  - Veterinary Oncology
    - Henry et al, JAAHA Mar 01
      - "Assay was not a useful predictor of response"
        - True of various non-lymphoid malignancies
        - True for LSA as well
    - NEW Imprimed assay – more ??'s than answers
    - Bottom line = Don't waste your money or time
- Use the new TK1 (Thymidine Kinase) assays?
  - I don't use them – Why?
  - Some reports suggest strong benefit for Dx/Px
    - Von Euler et al, JVIM 2004 & Int J Oncol 2009
    - Boye et al, JVIM 2018
  - Minimal to no benefit
    - Elliot & Blackwood, VetCompOncol 2011
  - Only beneficial when TK1 and CRP VERY high
    - Selting et al, JVIM 2016

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Canine Lymphoma – The Future

- Molecular diagnostics like PARR??
  - Burnett & Avery et al, Vet Path Jan '03
    - 91% PCR +, BUT 1/24 false positive (OOOPS!!)
    - Problems:
      - False positives!! 3 cases PCR + but did not have LSA
      - Ehrlichia may cause false positive! (Qurollo et al, JVIM '13)
  - Tamura K et al, Vet Immunol Immunopath '06
    - PCR on LN FNA's for Ig Heavy chain clonality; n=8
  - Hammer et al (Austria), VCO 2016; n =30 cats
    - Moderately helpful in B cell; POOR in T cell
  - Sensitivity & Specificity improving in cats
    - Rout & Avery et al, VetClinPath 2019
  - Bottom lines
    - Appears to need more study due to false positives & negatives
    - Only use when no other option – NOT GOLD STANDARD!
      - Keller, Vernau & Moore, Vet Pathol 2016

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Canine Lymphoma – The Future

Bone Marrow Transplants?

- VELCAP-HDC with autologous marrow
  - Frimberger et al, JVIM Mar 2006
  - 28 dogs with IV cytoxan dose escalation
    - MTD = 500 mg/m2 IV (normal dose is 200-250 mg/m2)
    - Median remission with HDC = 54 weeks
- Autologous transplant outcomes?
  - B's ~ 30% improvement (Willcox et al, JVIM 2012)
  - T's ~ 15% long term survival (Warry et al, JVIM 2014)
- Allogeneic bone marrow transplant
  - Single case report in JAVMA 2005
    - Done in conjunction with investigators at Fred Hutchinson CC
- BMT Programs
  - NCSU & VCA West LA – Latest Info?

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The Future (cont.)

- IS MORE CHEMO BETTER (than UW-25)?
  - Generally NO !!
    - CHOP-MA; Daters & Mauldin et al, VetCompOncol 2009
    - UW-25 with CCNU & MOPP; Rassnick et al, VCO 2010
      - 19 days longer 1st remission but much more neutropenia
    - Elspar/CHOP/Methotrexate; Sorenmo et al, VCO 2010
      - 7 month median remission but ~ 10% hospitalized
  - Development of Grade III/IV neutropenia?
    - Most common with elspar/vinc & vinc/cytoxan
    - Associated with prolonged first remission
      - Vaughn, Johnson & Williams, JVIM 2007
      - Sorenmo et al, Vet Comp Oncol 2010
- IS LESS CHEMO BETTER?
  - UW-12, 15 or 19?
    - Thamm et al VCO 2013 & 2015; Vos et al VCO 2019
    - Remission = 4.5 – 8 months; Why I STICK with UW-25 ☺
  - CHO vs CHOP? Zandvliet/Rutteman/Teske Vet '13
    - No difference in outcome – VERY interesting (N =81)

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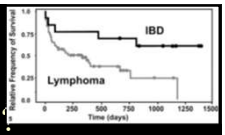
The Future (cont.)



- IBD vs LSA in CATS?
- Kiupel et al, Vet Pathol 2011
  - 63 cats with weight loss, vomiting and/or diarrhea
  - Examined histo, immunophenotype & clonality (COMBO BEST)
- Data on full thickness vs endoscopic Bx?
  - Synopsis = full thickness BEST
    - Freiche et al, JFMS 2016
    - Norsworthy et al, JAVMA 2015
    - Scott & Willard et al, JVIM Nov-Dec 2011

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The Future (cont.)

- Vomiting Normal in CATS?
- Norsworthy & Kiupel et al, JAVMA 2013
  - 100 cats with vomiting, diarrhea and/or weight loss
  - AbdUS = small bowel wall > 0.25-.28cm
    - Musc to submucosa ratio > 1 (Daniaux et al, JFMS 2014)
  - Laparotomy & full-thickness SI Bx's (6mm punch)
    - Pancreatic Bx did NOT = pancreatitis NOR increased fPLI
  - 49% IBD, 46% LSA, 3% MCT, 1% AdCa
  - Chronic/recurrent vomiting is NOT normal in cats!

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The Future (cont.)

- Indolent Lymphomas?
  - Valli et al, Vet Pathol May '06 (n = 66)
    - Marginal zone, Follicular & Mantle Zone LSA's
      - PCR tests = FALSE NEGATIVE in 20% of cases
  - Flood-Knapik & Sorenmo et al, VCO 2013
    - IHC changed Dx ~ 21% !!
    - T-zone LSA MST ~ 2-3 years with NO Rx!
      - Valli et al, VetPath '06 & '13
      - Seelig & Avery et al, JVIM '14 (Flow & Histo)
        - 40% = Golden Retrievers and all had LN's & Lymphocytosis – NEED FLOW & HISTO
    - Marginal zone (25%); MST 21 months
    - Chlorambucil/Pred >>> CHOP

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The Future (cont.)

- What are cats with IBD/LSA often low in?
  - Should we be testing for B12 more?
  - Should we automatically supplement ± retest?
  - Any others?
    - Lalor & Mellanby et al, JVIM 2014
      - 25-Hydroxyvitamin D
      - Worst in hypoalbuminemic cats
      - Other fat soluble vitamins? Pathogenesis? Rx ??
- Maitake PETfraction??
  - Griessmayr et al, JVIM 2007
    - N = 15; NO RESPONSES

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The Future (cont.)

- Immunophenotype:
  - Prognostic in almost every canine study to date
    - Flow vs PARR vs IHC??
      - Flow is BEST (Thalheim & Suter et al, JVIM 2013)
    - FLOW IS NOW A STANDARD OF CARE DIAGNOSTIC
- Novel & Rationally Targeted Therapies
  - Chemo for LSA has hit a "plateau"
    - Proteosome inhibitors, Vaccines, Others
    - CD40-Activated B cell Cancer Vaccine
      - No change in remission nor survival but helpful with rescue (small n!)
      - Sorenmo & Mason et al, PloS One 2011
    - CD20 Vaccine from Merial/BI?
  - Elspar/MOPP or LOPP for K9 T-cell LSA & ↑↑Ca^{++}
    - Brodsky et al, JVIM 2009; Brown et al VCO 2017; Morgon et al, VCO 2018
    - 90-98% overall response rate, PFS = 176d - 431d
    - Appears better than historical CHOP results
- Aratana Canine CD20 & CD52?
- Laverdia-CA1 from Anivive/Dechra?
  - New nuclear transport inhibitor – PO twice weekly

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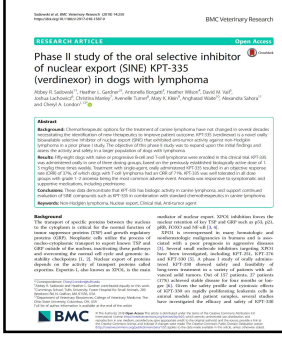
New Class of Drug

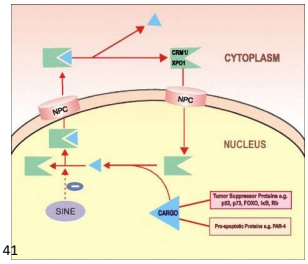
- **Selective Inhibitor of Nuclear Transport (SINE)**


BMC Veterinary Research

RESEARCH ARTICLE Open Access

Phase II study of the oral selective inhibitor of nuclear export (SINE) KPT-335 (verdinexor) in dogs with lymphoma

https://jhoonline.biomedcentral.com/articles/10.1186/s13045-014-0078-0



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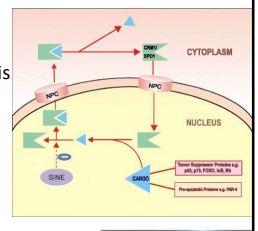
SINE Class Drugs- Background

SINE: selective inhibition of nuclear export

Selective inhibition karyopherin-β protein exportin 1 (XPO1)

- Functions to maintain cellular homeostasis
- Overproduced by neoplastic cells
- Recognizes specific nuclear export signal
- Exports > 220 proteins and RNA from nucleus to cytoplasm via nuclear pore complex (NPC)
  - –Tumor suppressor proteins (TSPs), growth regulatory proteins (GRPs), RNA



Azmi A, et al. Nat Rev Clin Oncol 2020:https://doi.org/10.1038/s41571-020-0044204

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Reasonable Expectation of Efficacy

Preclinical Evaluation of Verdinexor in Spontaneous Canine Cancer: Results of a Phase I Study

Phase 1 Study Design
This study was a dose escalating, open label assessment of the safety and biologic activity of verdinexor in client owned dogs with spontaneous malignancies. The initial dose of **1 mg/kg orally twice per week (Monday/Thursday orTuesday/Friday)** was based on previous data from normal laboratory dogs and dose escalation was set at 0.25 mg/kg increments in cohorts of 3 until dose limiting toxicity (DLT) was identified. Disease progression or signs and symptoms definitely related to disease were not considered adverse events (AEs). The maximum tolerated dose (MTD) was considered to be one dose below that at which DLT occurred.

Response To Therapy
The median TTP for all dogs was 35 days (range 14–246 days). A total of 7 dogs experienced PD in the first 4 weeks of therapy. Two dogs had a PR for 71 and 246 days, and 8 dogs experienced SD for a median of 58.5 days (range 28 – 84 days). Of these 10 dogs, 6 were receiving prednisone prior to starting verdinexor that continued during treatment and 4 did not receive prednisone during their treatment.

All but one of the dogs with clinical benefit (CB) associated with verdinexor administration (PR or SD > 4 weeks) had NHL with a median TTP in responding dogs of 66 days (range 35– 256 days).

The MTD was established as 1.75 mg/kg given twice per week with biologic activity at 1.0 mg/kg

MTTP: 35d
PD: n=7, within 4 weeks
PR: n-2, 71, 246 days
SD: n=8, median 58.5 d

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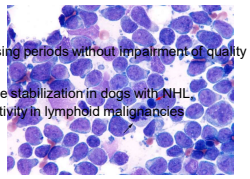
Based upon this data: Reasonable Expectation of Efficacy

Preclinical Evaluation of Verdinexor in Spontaneous Canine Cancer: Results of a Phase I Study



Conclusions
- Acceptable and tolerable side effects over prolonged dosing periods without impairment of quality of life
- Either objective response to therapy or prolonged disease stabilization in dogs with NHL, supporting the notion that XPO1 inhibition has biologic activity in lymphoid malignancies

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Clinical Efficacy

BMC Veterinary Research

RESEARCH ARTICLE Open Access

Phase II study of the oral selective inhibitor of nuclear export (SINE) KPT-335 (verdinexor) in dogs with lymphoma

	Objective Response Rate	Time to Progression	
Naive (n=35)	34.3% (12/35)	36.5 days	7-244 days
Relapse (n=23)	34.8% (8/23)	22 days	7-194 days
All Dogs	34.5% (20/58)	29.5 days	7-244 days

The Objective Response Rate (PR + CR): 34.5% (20/58)
T-cell lymphoma: ORR of 71%

The median TTP:
36.5 days (range 7-244) for naïve LSA
22 days (range 7-194) for relapse LSA

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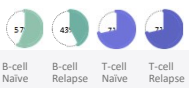
Efficacy Against All Types of LSA

LAVERDIA-CA1 efficacy was established in a study with 58 client-owned dogs with B- or T-cell lymphoma, naive cases or in first relapse after completing a single or multi-agent chemotherapy regimen. The study included dogs of varying breeds, weights, and genders with the majority of the dogs having stage III lymphoma.

Clinical Response (CR+PR+SD)

Phase 2 Study	N	PR/CR	Clinical Benefit	Duration of Benefit
All	58	20 (34%)	32 (55%)	71 days (21-273)
Naive B *	28	8 (29%)	16 (57%)	71 days (28-195)
Relapse B *	14	4 (29%)	6 (43%)	70 days (23-214)
Naive T *	7	4 (57%)	5 (71%)	42 days (21-273)
Relapse T*	7	4 (57%)	5 (71%)	72 days (30-194)

Overall Clinical Benefit



Overall Quality of Life

A validated health related Quality of Life (QOL) form used to assess dogs during treatment demonstrated that the overall QOL did not decrease in dogs during treatment supporting the notion that clinical toxicities associated with verdinexor are generally well tolerated.

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Proven Efficacy Against All Types of Canine Lymphoma

LAVERDIA-CA1 efficacy was established in a study with 58 client-owned dogs with B- or T-cell LSA, naïve cases or in first relapse.

The study included dogs of varying breeds, weights, and genders with the majority of the dogs having stage III LSA

Efficacy Data for Dogs Remaining on Study Past Day 56

Dog	Phenotype	Naive or Relapse	Objective Response	Duration Of CR/PR (days)	Time to Tumor Progression (days)	Study Duration (days)
01-01	B-cell	Naive	PR	14	70	126
01-03	B-cell	Naive			114	121
01-05	B-cell	Naive			73	80
01-06	B-cell	Naive	PR	14	70	195
01-07	T-cell	Relapse	PR	49	72	72
01-12	B-cell	Naive			71	85
01-13	B-cell	Relapse			112	112
01-14	T-cell	Relapse			56	56
02-01	B-cell	Naive	PR	21	105	105
02-05	T-cell	Relapse	CR	152	194	194
03-01	B-cell	Naive			21	67
03-04	B-cell	Naive	PR	36	71	71
04-01	B-cell	Relapse	PR	13	20	56
06-02	T-cell	Naive	PR	36	62	119
06-03	T-cell	Naive	PR	126	244	273
07-05	T-cell	Relapse	PR	21	42	103
08-01	B-cell	Naive	PR	43	71	71
08-05	B-cell	Naive	PR	98	182	182
08-06	B-cell	Relapse			84	84
08-07	B-cell	Relapse	PR	45	112	214

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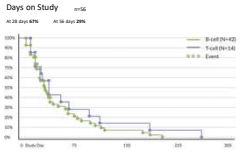
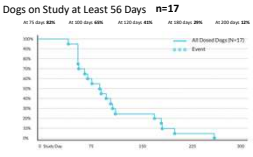
Proven Effectiveness

Proven Efficacy Against All Types of Canine Lymphoma

Days on Study n=56



Dogs on Study at Least 56 Days **n=17**



* Two of treated dogs were not immunophenotyped

At day 28, 67% (39/58) of dogs continued on study
A subset (17/58, 29%) TTP of at least 56 days.

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Adverse Events

Most Common Adverse Events Seen in Clinical Studies

Anorexia	n=27	45%
Weight Loss	n=18	31%
Vomiting	n=15	26%
Lethargy	n=10	17%
Diarrhea	n=7	12%

Most adverse events were considered Veterinary Cooperative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE)[1] Grade 1 (mild) or 2 (moderate).

Of the 58 dogs treated with verdinexor, adverse events occurring in less than 10% of dogs included:

- *Renal:* protein losing nephropathy, urinary incontinence
- *Hepatic:* hepatomegaly, elevated bilirubin, icterus
- *Cardiorespiratory:* heart murmur, arrhythmia, heart block
- *Hematologic:* hypoglobulinemia, hypoproteinemia, hypoalbuminemia, prolonged prothrombin time
- *Neurologic:* seizure, tremor, disorientation
- *Ocular:* corneal opacity
- *Skin:* bruising, erythema, alopecia
- *Other:* nasal discharge, epistaxis, lymphadenitis

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First-in-class Drug For Canine Lymphoma

NEW FIRST-IN-CLASS **SINE TECHNOLOGY**

LAVERDIA-CA1 (verdinexor) is the **first oral treatment** conditionally approved by the FDA for canine lymphoma

Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-526

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. It is a violation of Federal Law to use this product other than as directed in the labeling.

Targeted
Kills cancer cells at the nuclear core, generally sparing healthy ones

Effective
Proven efficacy in all types of canine lymphoma

Safe
Studies show only mild or moderate side effects

Convenient
Twice weekly at-home oral administration increase compliance

Affordable
Priced to expand your options and treat more patients

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When to use LAVERDIA-CA1

LAVERDIA-CA1 (verdinexor) Treatment Algorithm for Canine Lymphoma

Lymphoma Diagnosis

Discuss Referral and Treatments

Recommend Referral

Treated at Specialist

- Initial Therapy — Use in naive patients when CHOP or other cytotoxic therapies are declined
- Rescue Therapy — Use in relapse patients when CHOP or other therapies stop working or must be stopped due to side effects
- Integrated Therapy — Easily integrate into your existing lymphoma treatment protocol

Decline Referral

Treated at Primary Care Veterinarian

- Newly Diagnosed Patients — Use as treatment for patients who decline a specialist referral or have concerns about the side effects of traditional chemotherapy
- Relapse Patients — Use as rescue therapy post CHOP or other chemotherapy initiated by specialist to provide ongoing care
- Palliative Care Patients — Use as targeted therapy for patients who otherwise choose palliative care

"Verdinexor could give veterinarians another option if first-line chemotherapy fails or as a potent adjunctive therapy."

—Cheryl London, DVM, PhD, DACVIM (O)

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Dosing

Convenient Oral Administration

Initial Dosing: **1.25 mg/kg** given twice per week with at least 72 hours in between doses.

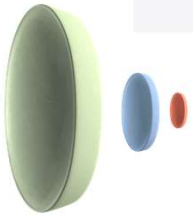
If tolerated after two weeks, increase the dose of LAVERDIA-CA1 to **1.5 mg/kg** twice/week with at least 72 hrs between doses.

Color Coated Tablets

Allows for safe at-home administration and easy identification of tablet strength.

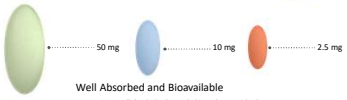
Precise Dosing

Three tablet strengths allow for precise dosing for each patient to maximize the therapeutic benefit while minimizing side effects.



Purposeful Pill Design

Three Tablet Strengths



Feed Before Administering

Dogs should be fed immediately before giving LAVERDIA-CA1. Time to maximum plasma concentration is between 1.1 and 2.5 hours post-dose under fed conditions.

Well Absorbed and Bioavailable

LAVERDIA-CA1 is well absorbed in dogs and achieves therapeutic levels (>0.5 to 1.0 µM) with doses of 1 to 3 mg/kg. There is a significant food effect on the pharmacokinetics of LAVERDIA-CA1 with a 3-fold and 5-fold increase in AUC and Cmax, respectively.

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Safe Handling Instructions

Wear protective disposable chemotherapy-resistant gloves when handling LAVERDIA-CA1

Wash food and water bowls separately from other items during treatment and for three days after the dog has received the last treatment

Prevent direct contact with moistened, broken, or crushed LAVERDIA-CA1 tablets

Prevent contact with patient's feces, urine, vomit, and saliva during treatment and for three days after the dog has received the last treatment

Pregnant and nursing women, children, and breeding dogs should not handle LAVERDIA-CA1

Do not store near food in or near a food preparation area, or with medications intended for human use

Do not eat, drink or smoke while handling LAVERDIA-CA1

Remember to give your clients chemo resistant gloves and waste pickup bags

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How to Monitor?

Based on laboratory as well as field safety and efficacy studies, no Laverdia-CA1 specific monitoring is required.

In clinical trials, dogs were evaluated weekly for 4 weeks after starting treatment and then every 2 weeks thereafter.

It is recommended that appointments for routine monitoring, periodic physical exams, and blood work be scheduled as needed based on the patient's response to treatment.

Evaluation after 2 weeks of treatment would be prudent to assess whether a dose adjustment could benefit the patient.

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There is good science behind the product

The technology of LAVERDIA-CA1 is supported by extensive scientific publication as well as broad clinical research.

Peer-Reviewed Journal Articles:
SINE Technology 162
Verdinexor 14



A

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What do I think about this drug?

- The Data is limited, small number of total cases
  - Difficult to draw too many conclusions….but….
- First in class drug with proven efficacy in physician-based oncology
  - This also means there will be a learning curve regarding ***Laverdia CA-1***
    - Good and bad about a CA-1 designation
    - What cases to use
      - Naïve, Relapse, Atypical cases??
      - Bias when used as a last resort….

» "Oh this drug doesn't work"…how many times have you used it?…."1 case"

    - Should dose be adjusted and when?
    - Combining with chemotherapy? If so which drugs and how?
      - THIS is the likely largest impact of this drug
    - How best to handle side effects
    - Investigator driven trials WILL help find its niche…..

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What do I think about this drug?

- GREAT to have another drug in the toolkit!
- Convenient, oral drug, 2x weekly
- Monitoring is relatively easy vs other agents
- Relatively cost effective option for owners who can not afford standard of care
  - May open an avenue for dogs who otherwise would not have received care (expanding access)
  - In the end this may translate to more cases receiving therapy (unmet need)

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What do I think about this drug?

- Data is interesting on several points
  - High response rate for T cell (which we are still struggling to find a valuable drug for)
  - Several dogs (n=20) were on the drug > 56 days
    - A subset had progressive disease (per trial assessment), but stayed on drug and had a clinical benefit for many weeks
    - ***Need to find out who this subset is…..***
    - Understanding clinical benefit (stable disease)
      - Not something we are used to with LSA, generally respond or progress, no middle ground
  - ***Take away point: Maybe don't jump off drug too quick?***

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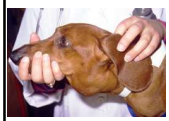
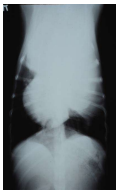
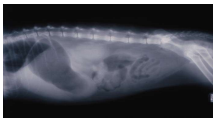
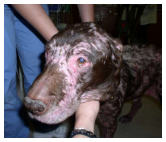
Where does Laverdia-CA1 Fit In ?

- Label is very broad
  - Can be used for ANY canine LSA :)

Naive

Relapse

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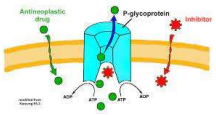
Where does Laverdia-CA1 Fit In ?

- Naïve setting:
  - Owner declines referral but wants more than prednisone
  - Owner is deciding whether to treat or can't get into the oncologist for weeks
  - ***Does not appear to induce MDR, reduces the risk if they change their mind***
- Relapse setting:
  - Owner elects against more aggressive protocols
  - Patient has run out of therapy options and owner is simply looking for more time
- T cell LSA
  - Appears to have ± better activity in T than B!
  - Multicentric, Epitheliotropic, Indolent, Atypical
- Maintenance Setting post CHOP?? During CHOP??
  - Investigator initiated studies will answer



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Where does Laverdia-CA1 Fit In ?

- Can I use "off label" in dogs?
  - –Big fat no!
- Can I use it in other species?
  - –Big fat no!!

No!

No!

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Conclusions

- More aggressive Rx
  - = longer remission & survival times
  - Remember there is a LIMIT!!
- Use a protocol you are:
  - familiar with & comfortable with
- What do I use??
  - UW 25 week as first line (CHOP works best!)
    - Great mix of lengthy remission with mild toxicity in dogs
      - Appears to be working same or better than UW-19
    - Less activity in cats
    - Add in MOPP for T cell LSA's
  - Fall back to other protocols due to constraints
    - Pred vs COP vs Adria alone
    - "Oral only" = CCNU, Cytoxan, pred, Laverdia-CA1
      IV chemo is NO more toxic than oral chemo
    - $$$ constraints = CCNU/pred or cytoxan/pred or Adria X 5

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Conclusions

- KNOW YOUR prognostic factors ☺
  - DOG: Substage, grade, B vs. T, anatomic location, age
  - CAT: Substage, FeLV, Response to Rx
- Staging is helpful to determine prognosis
  - Don't use up entire $$$ for staging though!!
- REMEMBER
  - Each patient is different
    - No single BEST protocol
  - Discuss variety of options with client
    - Tolerance for # of visits and risk of toxicity
  - Need for better therapies is HUGE !!

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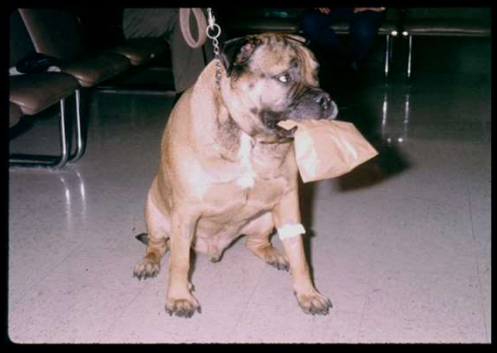

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