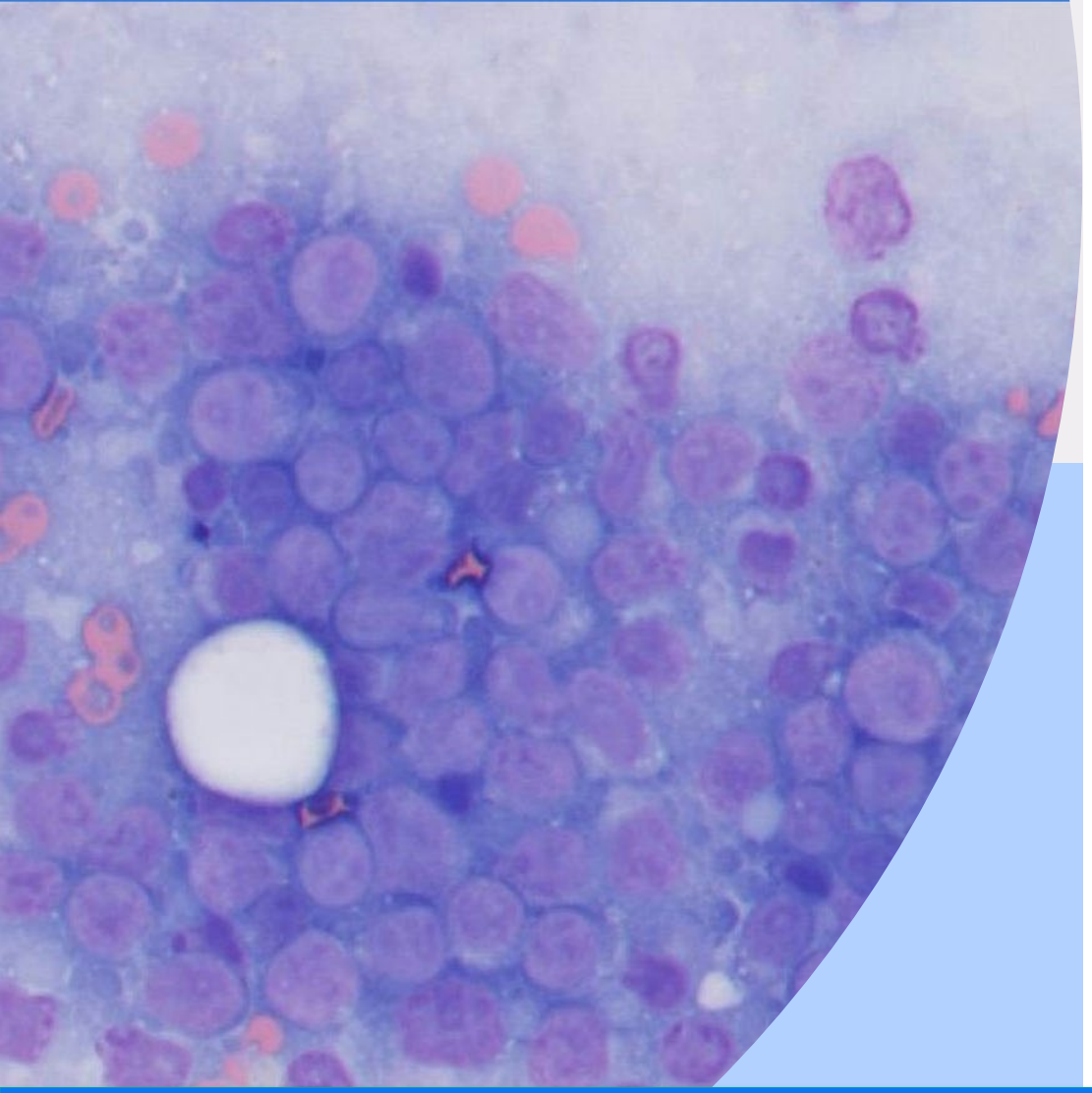

CREATING CLARITY

Avoiding the "bumpy"road on the path to treating lymphoma

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Oncology Consultant, IDEXX UK & Spain

Canine multicentric lymphoma (LSA)

- Epidemiology
- Clinical presentations
- Classification / Biological behaviour /Prognosis
- Diagnostic tests
  - Cytology and ancillary tests
  - Histopathology and Immunophenotyping
- **Treatment and prognosis**

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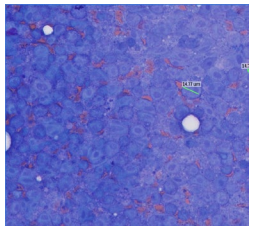
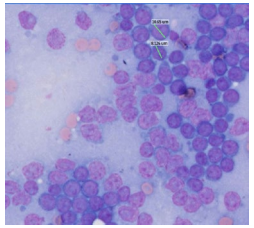
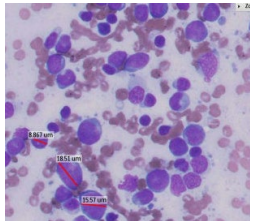
WHO classification of K9 multicentric lymphoma and prognosis: what do we know?

B-cell lymphomas





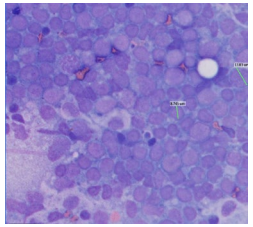


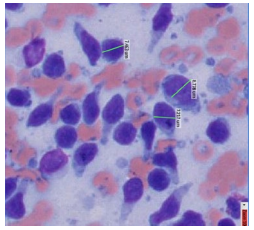
- **Diffuse large cell lymphoma**
  - Centroblastic
  - Immunoblastic
  - Anaplastic
- T-cell rich B-cell lymphoma
- **Marginal cell lymphoma (I)**
- **Follicular lymphoma (I)**
- Lymphoblastic B-cell lymphoma

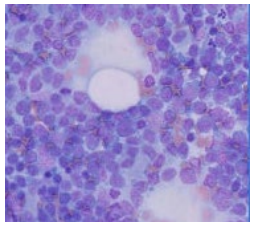
Pics credit: Dr Wheeler; IDEXX

T-cell lymphomas

- Lymphoblastic T-cell lymphoma
- **Peripheral T-cell lymphoma, not specified**
- **T-Zone lymphoma (I)**
- T-cell lymphoma associated enteropathy
- Mycosis fungoides
- Hepatosplenic T-cell lymphoma
- T-cell lymphoma associated with panniculitis







Entities recognized by the ACVP lymphoma working group.

(Valli et al. 2011.)

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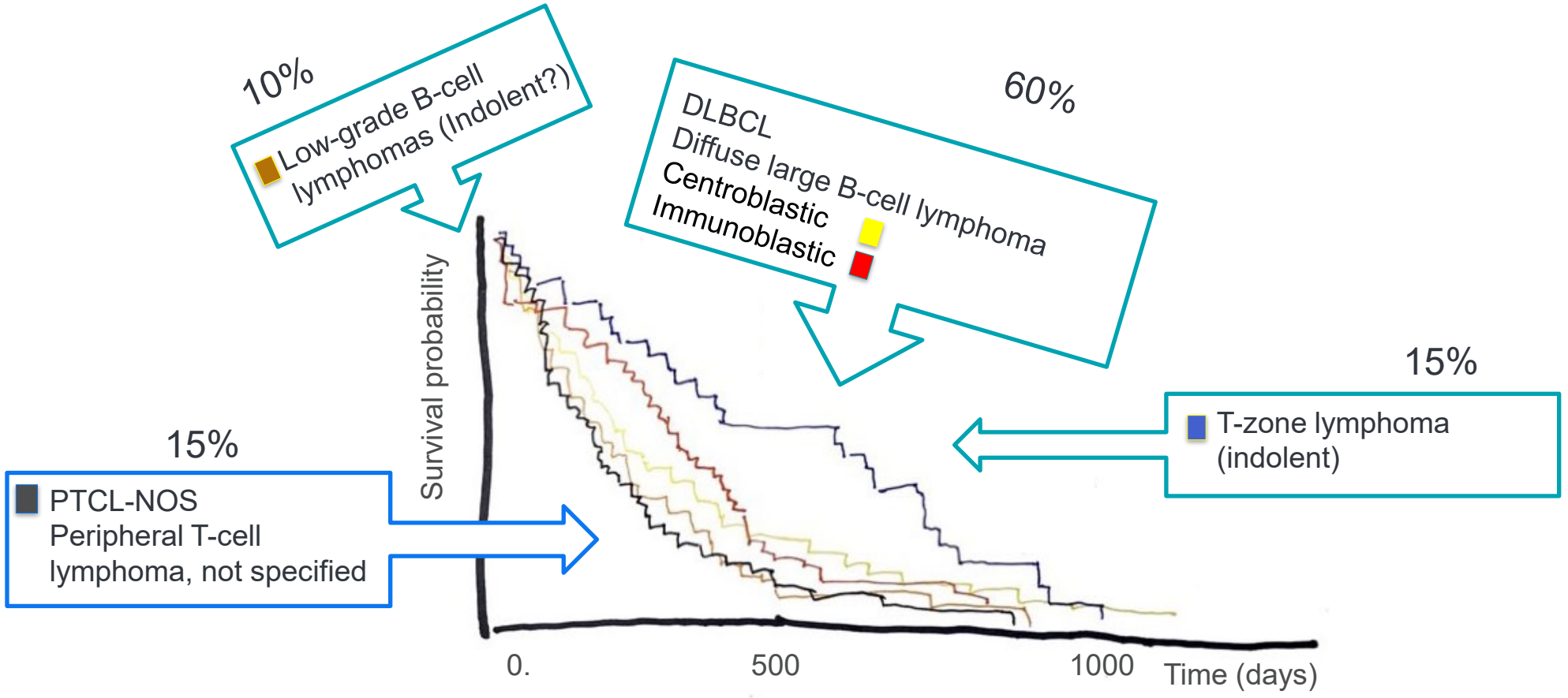
WHO classification of K9 multicentric lymphoma and prognosis: what do we know?

Association between WHO classification type, disease stage,tumor subtype, mitotic rate and treatment with survival in 456 dogs!!



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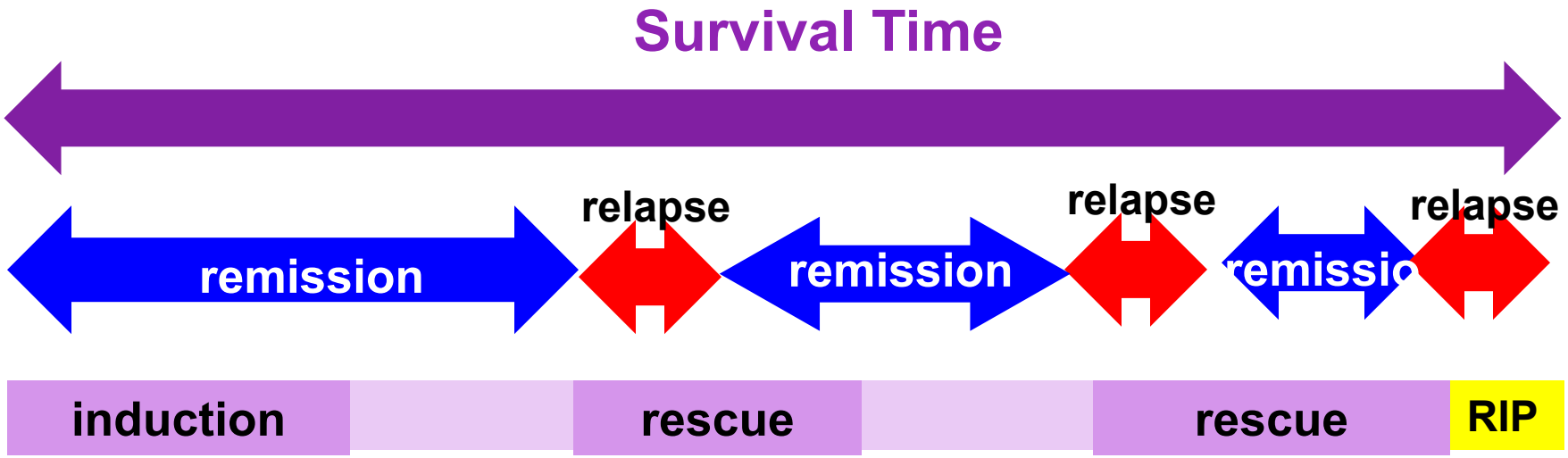
Valli et al. 2103

LSA basic concepts: remission (PFI) vs survival (MST)

Overview of biological behaviour and therapy of Canine Lymphoma (multicentric)



- MST=median survival time Average survival multicentric high grade LSA with steroids <2 months
- PFI= Progression free interval

(Rassnick et al. 2021.)

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Diffuse large B-cell LSA (DLBCL) considerations

- This is the most common type of multicentric lymphoma
- 50-60% of cases
- Response rate to COP (vincristine, cyclophosphamide, prednisolone) or CHOP protocols (vincristine, cyclophosphamide, doxorubicin, prednisolone) close to 90%, mostly complete
- Previous studies mixing together all LSA types! Estimated remissions of 1 y
- Was that accurate? Any specific studies about DLBCL?

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Diffuse large B-cell LSA progression free survival

Median remissions 8.5 months with CHOP 19-25 wks (4-6 months therapy)

- COP (8-week) – remission 5 months
- Remission with longer COP ?

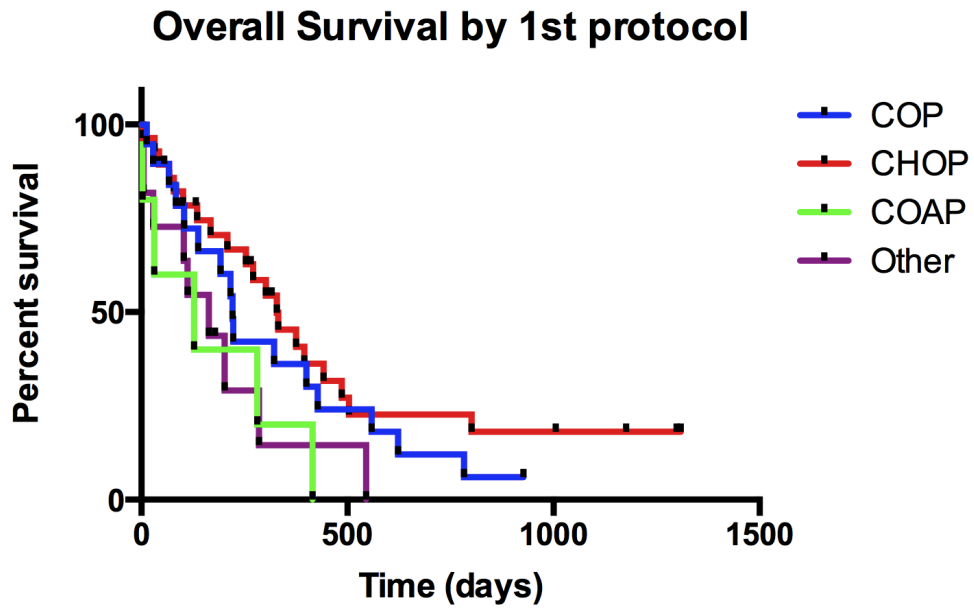
- No effect on survival rates:
  - Stage and substage at diagnosis
  - Induction protocol if DOXO used at first rescue

Positive prognostic factors

- Complete response
- Duration of first remission
- Use of **Rescue protocol!!!** MSTs >13 month

Negative prognostic factors

- No rescue
- Thrombocytopenias, neutrophilia



MST with rescue protocol 412 d

(Davies et. al 2018, Childress et al 2018, Wolf-Ringwall et al. 2019)

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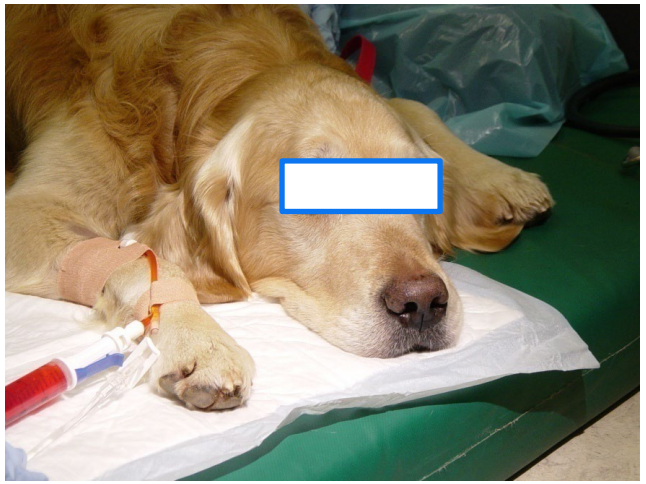
Doxorubicin single agent for high grade B-cell LSA

- *4-6 doses total – q 3 wks*
- Response rate 84%
- Progression free interval 147d
- Survival 182d
- 1y survival rate 23%
- Doxorubicin as needed…
- Response rate 67% and remission 65=80d



(Al-Nadaf et al. 2018; Higginbotham et al 2013)

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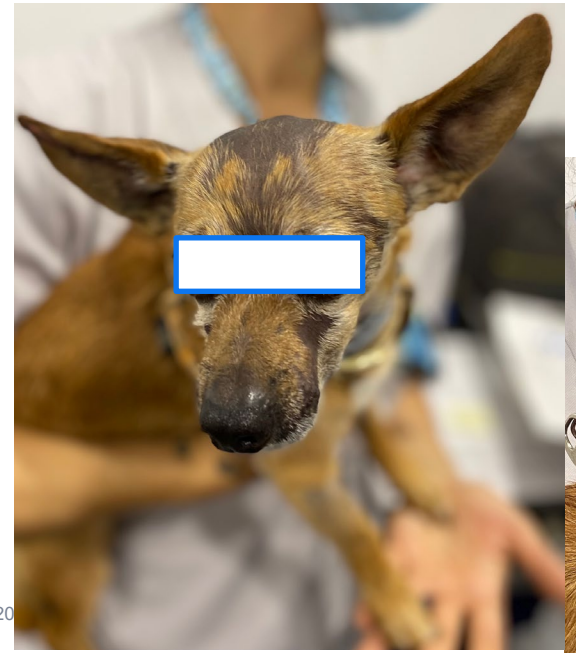
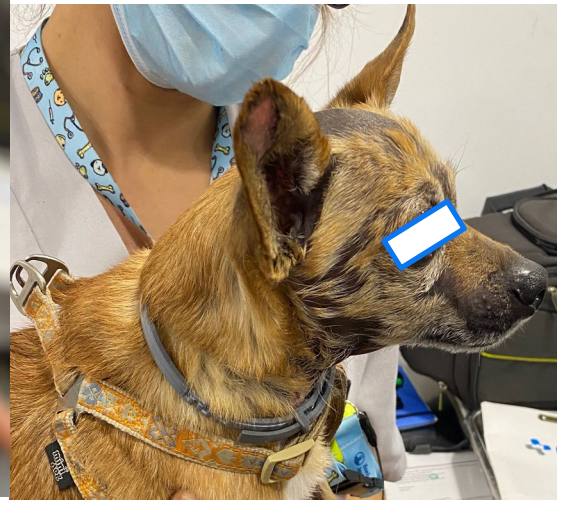
Novel therapeutics for B-Cell LSA

TANOVEA™-CA1 (rabacfosadine) (GS-9219, VDC-1101)

- Novel pro- drug of 9-(2 phosphonyl-methoxyethyl) guanine (PMEG),
- Used in naïve and relapsed multicentric lymphoma, alone and with doxorubicin
- Practical level best results scenario = **relapsed** B-cell lymphomas
  - Response rate 74% with 45% Complete remission – 7 months
- Expensive
- Specific toxicities (cutaneous, pulmonary fibrosis, low prevalence)





(Thamm et al. 2017; Saba et al. 2018)

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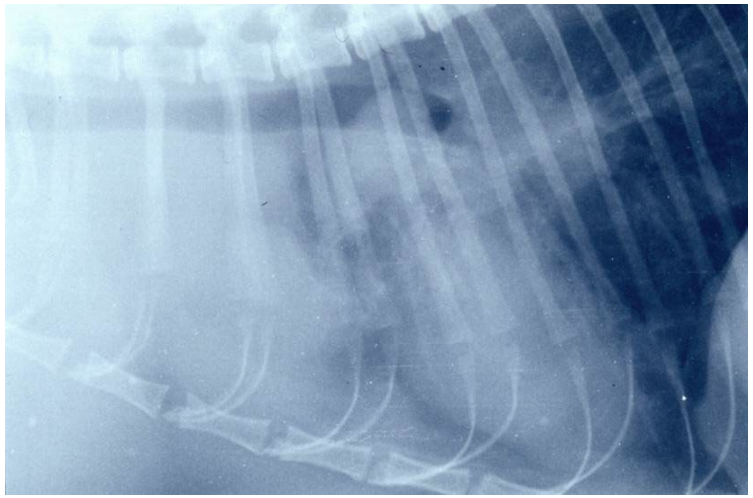
Non Indolent T-cell lymphomas



- Peripheral T-cell LSA (PTCL-NOS) 15%
- Anaplastic T-cell LSA 5%
- Most high grade = Rapid progression
- Complex clinical presentation - mediastinal mass,internal, hypercalcemia, extranodal
- Inherent resistance to doxorubicin (50% response rate <20% complete) (Beaver et al. 2010)
- Short remission/survival times with CHOP - rapid resistance to chemo

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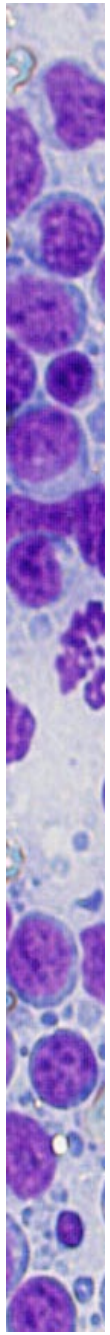

Non Indolent T-cell lymphomas
(PTCL-NOS/anaplastic T-cell LSA)

- Protocols with alkylators = Higher responses and Longer remission
- LOPP feasible in practice (vincristine, lomustine, pred and procarbazine (or cyclophosphamide)
- MOPP or VELCAP-TSC (also mechlorethamine, dacarbazine…)
- Response rates 70-97%
- Recent studies with LOPP median remission 5-6 months
    - Complete response 60% with remissions ~10 months
    - Non-responders MST 3 months
- Hypercalcemia + prognostic factor

(Brown et al. 2017, Goodman et al. 2018, Purzycka et al 2020, Blaxill et al. 2021)

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Novel therapeutics for T-Cell LSA

Verdinexor
Laverdia KPT-335

- **Selective inhibitor of nuclear export (SINE) that blocks chromosome region maintenance 1 (CRM1).**
- 58 dogs with naïve or progressive B-cell and T-cell lymphoma
- T-cell lymphoma: response of 71% vs. overall 37%
- Short-lived time to progression ~ 2 months

Citation?

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Indolent Lymphoma B-cell

Around 10% of multicentric LSAs. Histology required

Marginal zone LSA.

Splenic more common and good to excellent prognosis

Nodal – one LN / multicentric Survival 7-9 months with CHOP

- Scarce literature. Best therapy to be defined
- Surgery if only one node affected
- Behavior not so indolent as T zone LSA ….or late diagnosis

Multicentric follicular and mantle cell LSA – very limited information

(Marconato et al. 2019)

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Increasing survival – rescue therapy

Indication: Relapse

- Complete response ≈50-70%
- Length ≈50%

If dog not on treatment at relapse, then repeat induction protocol:

- Madison Wisconsin (CHOP), COP or LOPP

If dog is on treatment, then use rescue protocol with new drugs:

- Lomustine + asparaginase
- DMAC (actinomycin D, cytarabine, melphalan, corticosteroids)

- **Not much variety in rescue protocols other than Tanovea in the past 10-15 years**
  - Usual median remission times are 2-3 months for 2nd rescue or beyond
  - 4-6 months for dogs with a complete response

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Conclusions

- A diagnosis of lymphoma should include morphologic classification according to WHO or at least immunophenotype and grade to predict prognosis and provide best treatment
- Refining diagnosis rather than extensive staging allows investing budget in the most appropriate treatment
- Successful cases will live longer when treated upon relapse

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