Pharmacokinetic and Pharmacodynamic Considerations in Cancer Chemotherapy

Indications and Dosing

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Outline of Discussion

- Pharmacokinetics
  - Parameters
  - Variability
- Pharmacodynamics
  - Toxicity
  - Efficacy
  - Surrogate Measures of Response
- Dose Normalization
  - Per kg, per m^2
  - Other dosing metrics
- Drug Dosing of Specific Agents
  - Dose finding studies
  - Selecting the proper dose, dose interval and what to measure

Pharmacokinetics (PK) and Pharmacodynamics (PD)

How are they related?

Pharmacokinetics

- The fate of a therapeutic agent when administered to a living organism
- Commonly described by drug levels measured in the blood compartment

Pharmacodynamics

- The effect of a therapeutic agent in a living organism
- Commonly described by clinical endpoints

Pharmacokinetics and Pharmacodynamics

- Through Drug Exposure at the Site of Action

Is Dose Proportional to Exposure?

In general, drug exposure is proportional to dose. However, notice the variability in exposure across the population.

Dose \( \rightarrow \) Exposure \( \rightarrow \) Response

Data from 20 dogs treated with Doxorubicin @30mg/m^2 via a 20 minute infusion

Pharmacokinetics

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- Commonly described by drug levels measured in the blood compartment

Pharmacodynamics

- The effect of a therapeutic agent in a living organism
- Commonly described by clinical endpoints

Dose \( \rightarrow \) Exposure \( \rightarrow \) Response

PLoS One 5:e11013, 2010

Data from 28 dogs treated with Doxorubicin @30mg/m^2 via a 20 minute infusion

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Dose \( \rightarrow \) Exposure \( \rightarrow \) Response

Common Assumptions of Drug Therapy

- Dose is related to drug exposure
  - Higher dose leads to proportional increase in drug exposure
- Drug exposure is related to response
  - An increase in drug exposure will increase drug response, both good and bad
  - Blood/serum/plasma drug levels are a good indicator of drug exposure
  - Circulating levels of drug in the blood are proportional to "target tissue" drug levels

Dose \( \rightarrow \) Exposure \( \rightarrow \) Response

Data from 28 dogs treated with Doxorubicin @30mg/m^2 via a 20 minute infusion

In general, drug exposure is proportional to dose. However, notice the variability in exposure across the population.

Dose \( \rightarrow \) Exposure \( \rightarrow \) Response
Pharmacokinetics

IV bolus/short infusion administration of infrequent doses

• Measured Parameters
  • C<sub>max</sub> – maximal concentration achieved
  • AUC – drug exposure as determined by concentration x time
  • Terminal Half-Life – how long it takes drug to decay in the blood

Pharmacokinetics

Multiple Doses Given Frequently

• Measured Parameters
  • C<sub>max</sub>
  • T<sub>max</sub> – time to reach C<sub>max</sub>
  • Terminal half-life – plays a role in dosing interval and accumulation
  • C<sub>min</sub> – also referred to as trough

C<sub>max</sub> is a function of dose, t<sub>1/2</sub> and Tau
C<sub>min</sub> is a function of dose, t<sub>1/2</sub> and Tau
C<sub>avg</sub> is a function of dose, t<sub>1/2</sub> and Tau
Accumulation factor is dependent on t<sub>1/2</sub> and Tau
T<sub>max</sub> is dependent k<sub>abs</sub> and t<sub>1/2</sub>

How can C<sub>avg</sub> be the same but C<sub>min</sub> and C<sub>max</sub> be different?

Pharmacokinetics

Pro-Drugs

• Many clinically-used anti-tumor agents are actually pro-drugs and need to be activated in one way or another.

What should you actually measure?

Pharmacokinetics

Cyclophosphamide PK in Cats

PK of CP and 4-OHCP is similar in cats as 4-OHCP exposure is similar via the IV or PO route

Pharmacokinetics

Variability – Doxorubicin Exposure

Doxorubicin dosed at 30 mg/m<sup>2</sup> in dogs shows an exposure range in 20 dogs that can vary by ~2X.
In this cohort, there was no measured variable that could account for any of the variability.

Where does the variability come from?
- For doxorubicin this is a bit unclear
- Inter-patient variability (CV%) ~ 24%
- Intra-patient variability (CV%) ~ 18%
Pharmacokinetics
Variability – Doxorubicin Exposure

What does this mean?
• Adjusting DOX dosing based on renal or hepatic function has not been established
• DOX metabolism to DOXol does not correlate in any meaningful way with exposure but the combination of DOX + DOXol may be more informative than just DOX
• DOX exposure is related to dose but high intra-patient variability makes dose adjustment difficult within a patient

Pharmacokinetics
Variability – Vinblastine

Consequences of high variability
• Higher fractions of patients fall into exposure ranges that may result in less than optimal responses and more serious toxicities
• More complex dosing metrics are needed that attempt to reduce variability
• Without knowledge of inter- vs. intra-patient variability, dose escalation or reduction within a patient is difficult to interpret

Dose → Exposure → PD → Response

Pharmacokinetics
Variability – Vinblastine

PK Parameters following a dose of 2.5 mg/m²
IV bolus dose of vinblastine sulfate in dogs

Pharmacokinetics
Variability – Vinblastine

Dose-Exposure-Response

Drug effect is related to drug exposure... even for oncology.

Pharmacokinetics
Is Dose Related to Response?

In oncology this is a tough one... Dosing and drug exposure is usually limited to not elicit a toxic response, which is presumably related to therapeutic response. In general, it is assumed that dose intensity will correlate with response.

Pharmacokinetics
Is exposure related to response?

Drug exposure is related to response in the most direct manner and as such being able to predict drug exposure from a given dose would be the most exact way to have a more uniform dose-response relationship across a population.

This study in humans shows a clear relationship between exposure to vinblastine and the % decrease in absolute neutrophil count at the nadir within the cycle.
Relationships Between Drug Exposure and PD Response

Drug Toxicity as an Endpoint

Pharmacodynamics
Toxicity as an Endpoint

In human cancer drug development, toxicity is an endpoint that is defined in Phase I trials. The majority of chemotherapy drugs used in veterinary medicine have not undergone controlled clinical trials or what are commonly referred to as "Registration Trials" to define the indication of a specific drug. The off-label use of these drugs means that the dosing commonly used are based on a compilation of information from the combined experience of the veterinary oncology community.

Toxicity and Response to Chemotherapy

Pharmacokinetics
Do we even need PK?

This argues that:
1. Toxicity and efficacy are interrelated
   a) Presumably by exposure
2. Dose to toxicity
3. Response is the only metric you need

Pharmacokinetic/Pharmacodynamic Relationship

What do we need to make the best prediction within a patient with regards to dose-response?

1. PK data/modeling to predict exposure from a given dose to an individual
   - Data-based models that rely on sampling
   - Correlations between dose-exposure and patient characteristics (PopPK)
2. PD data/modeling to predict response from drug exposure to an individual
   - Data-based models that rely on sampling
   - Known relationships between exposure and response based on known patient characteristics

Limited Sampling Model to Predict DOX Exposure

Calculate exposure without full time course sampling

Development of a limited-sampling model for prediction of doxorubicin exposure in dogs

This allows for drug exposure data to be calculated with only 3 samples being collected within the first hour of treatment. This leads to an increase in compliance as patients need only be in the clinic for an hour after the end of drug infusion for all samples to be collected. Much better than having a full time course of samples collected over 6 hours.
PK/PD Relationships
Hematologic Toxicity of DOX

- Using the limited sampling approach for DOX prediction of exposure (AUC), 44 dogs were enrolled in a trial looking at DOX AUC and hematologic toxicity.

DOX exposure negatively correlated with WBC and neutrophil count.

Exposure – PD Relationship
Hematologic Toxicity of DOX

Using the information that DOX AUC and baseline neutrophil count are significantly correlated with the degree of neutropenia, a model was developed to predict the ANC at nadir based on these values.

What does this potentially allow you to do?

1. Treat with DOX at a standard dose (30 mg/m²)
2. Collect 3 PK samples within the first-hour
   - Have samples measured for DOX
   - Calculate AUC
3. Calculate out expected ANC at nadir
4. Adjust dose to target ANC at nadir based on DOX exposure and baseline ANC

Based on the relationship between neutropenia following therapy and length of first-remission shown in multiple studies, this type of approach should lead to better outcomes.... Of course a prospective trial with some type of dose adaptation is the ideal way to test this.

Let's take a 10 minute break

Dosing Calculations and Metrics

- Where the heck do these doses come from and why do we dose based on surface area?

1. Body surface area (BSA) dosing is based on the assumption that drug clearance correlates with BSA
2. There is an assumption that individuals of different sizes should be given different doses
3. The calculations used for estimating BSA in both humans and animals are based on very small sample sizes and have highly questionable accuracy in relating weight and height/length to a measure of BSA
4. Studies in humans have effectively shown that BSA dosing cannot account for an appreciable amount of variability in PK.
There is an assumption that individuals of different sizes should be given different doses

**This is more important in veterinary medicine... Why?**

The variability from the small to the x-large group is 50%-80% and this is excluding the two extremes. (Small and X-Large) — It is hard to assume that a dachshund and a rottweiler should get different doses... even though they might have the same colors.

Human range in height may be 20%, but looking at averages within groups... Weight is probably a bit wider due to variability in body shape.

Studies in humans have effectively shown that BSA dosing cannot account for an appreciable amount of variability in PK

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/kg/mtb/height</th>
<th>Tumor type</th>
<th>Recommended</th>
<th>Conclusion</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Etoposide</td>
<td>100 mg/m²</td>
<td>Standard</td>
<td>Fixed dose</td>
<td>Dose is wrong</td>
<td>[46]</td>
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<tr>
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<td>Metastatic</td>
<td>Fixed dose</td>
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<td>[47]</td>
</tr>
<tr>
<td>Paclitaxel</td>
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<td>Standard</td>
<td>Fixed dose</td>
<td>Dose is wrong</td>
<td>[48]</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>50 mg/m²</td>
<td>Metastatic</td>
<td>Fixed dose</td>
<td>Dose is wrong</td>
<td>[49]</td>
</tr>
<tr>
<td>CRT</td>
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<td>Fixed dose</td>
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<tr>
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<td>[51]</td>
</tr>
<tr>
<td>Imitrex</td>
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<td>Other</td>
<td>Fixed dose</td>
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<td>[52]</td>
</tr>
</tbody>
</table>

*The calculations used for estimating BSA in both humans and animals are based on very small sample sizes and have highly questionable accuracy in relating weight and height/length to a measure of BSA.*

**Humans**

Most commonly, BSA is calculated using the DuBois and DuBois equation:

\[
\text{BSA} = \left( \frac{\text{Weight} \times \text{Height}}{3600} \right)^{0.425}
\]

- Based on measurements made on 9 patients in the early 1900's.
- \( \text{BSA} = 0.00706 \times \text{weight}^{0.425} \times \text{height}^{0.725} \)
- But, more than 25 BSA formulae exist and they can give wildly different measures...

**Veterinary Medicine**

Equations used are not based on large studies and which equation is used can lead to disparate calculations of dose. Further, the calculations is only based on weight and does not take into account other variables in size.

**What About Other Metrics for Dose Calculation/Normalization**

<table>
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<tr>
<th>PK</th>
<th>Exposure</th>
<th>PD</th>
<th>Response</th>
</tr>
</thead>
</table>

- Size (kg or BSA)
- Organ Function
- Metabolism
- Transporters
- Co-Medications
- Sex

There are some major differences in vet area... but, using a continuous variable (per kg) as opposed to a binomial (small, medium, large) may make sense.

*The variability in the small to the x-large group is 50%-80% and this is excluding the two extremes. (Small and X-Large) — It is hard to assume that a dachshund and a rottweiler should get different doses... even though they might have the same colors.*

Human range in height may be 20%, but looking at averages within groups... Weight is probably a bit wider due to variability in body shape.
Dose Normalization Based on Organ Function

Carboplatin dosing in humans

For carboplatin dosing a target AUC is chosen and the dose in mg calculated based on the known relationship between dose/AUC and glomerular filtration rate.

If you round and solve for dose:

Dose (mg) = AUC (mg/mg/min) \times (GFR)(ml/min) \times 22.5 (ml/min)

Study Design and Drug Dosing and Administration

Patients were enrolled at institutions who work with dogs. For all samples, will be administered intravenously (i.v.) at 100 mg/m² over 3 hours followed by carboplatin at once under the same (i.v.) with (mg/kg) every 21 days for 3 cycles, MAP: 90 mmHg. AUC:

Serum

Bone Marrow

Gut

This same relationship holds in cats!

Doxorubicin dosing in humans

Tissue exposures were simulated by PBPK modeling.

Dose Calculation based on Transporter Polymorphism

As we learn more about drugs in veterinary populations and as we learn more about individual differences between breeds and species, this information will be incorporated into dosing decisions.

Population PK Analysis

Bottom Line on Dose Normalization

How we got where we are with some specific drugs used in veterinary oncology

- Doxorubicin
- Cyclophosphamide
- Vincristine/Vinblastine
- Lomustine
- Carboplatin
- Toceranib

Doxorubicin

Basic Pharmacology

- Widely distributed to tissues
- Metabolized hepatically and extra-hepatically
- Single most active agent used in veterinary oncology
- Toxicities include GI, hematopoietic, and cardiac toxicity associated with total dose
- Can cause severe local tissue damage with extravasation

Mechanism of Action

- Inhibition of RNA and DNA polymerases
- Topoisomerase II inhibition
- Alkylation of DNA
- Reactive oxygen generation
- Perturbation of cellular Ca²⁺ homeostasis
- Inhibition of thioredoxin reductase
- Interaction with plasma membrane components
Doxorubicin Dosing in Dogs
Toxicity as an endpoint for dose selection

Toxicity (or avoidance of) is inherently the PD endpoint for the current use of cancer chemotherapy in companion animals... Why?

Where did the dose of 30 mg/m² for doxorubicin in dogs come from?

First report that I can find of that dose is from:

And they cite the selection of that dose from these studies:

Doxorubicin Indications and Dosing

Most active single agent available
- Lymphoma – single agent or combo (CHOP)
- Osteosarcoma – single agent or combo (carbo)
- Mesenchymal Tumors
- Epithelial Tumors

Doxorubicin Specific Considerations
- Extravasation Damage
- Vigilant observation during infusion
- Dexamethasone for treatment
- Severity may require surgery and potential amputation
- Cardiac Performance and Monitoring
  - Evaluate to detect new murmurs, arrhythmias or pulse deficits
- Cumulative Dose
  - Ostenisibly limited to 120-150 mg/m² due to cumulative cardiac damage

Cyclophosphamide

Basic Pharmacology

Mechanism of Action
- Binding to DNA
- Cross-linking of DNA through bifunctional alkylation

- Can be dosed IV, PO or IP
- Major dose-limiting side effects are neutropenia and thrombocytopenia
- GI toxicity is not common in dogs but has been observed in cats
- Hemorrhagic cystitis is uncommon at standard doses but has been observed

Cyclophosphamide Use in Animals

The Cornell Veterinarian

First reported use of CP is treating dog cancers was for treating generalized lymphoma in 1962. They observed some response to the drug in a dog of 2.5 mg/kg. The drug was widely studied in dogs in the 60’s and 70’s for use in organ transplants via immune suppression. Toxicity and efficacy come from those studies as well as studies in dogs with lymphoma and other neoplasms.

Cyclophosphamide Indications and Dosing

Indications
- Lymphoma in dogs (CHOP)
- Lymphoma in cats

Conventional Dosing
- Boli by IV or Oral (PO)
  - 250 mg/m² q3w in dogs
  - Fractionated
    - 50mg/m² 4-3 days
  - 200-250 mg/m² IV in cats
  - Up to 300 mg/m² PO in cats

Cyclophosphamide Specific Considerations
- Hemorrhagic Cystitis
- Furosemide is generally given prior to IV treatment
- Vigorous hydration
- Frequent urination
- CP should be discontinued if cystitis occurs
- Chlorambucil can be used as a substitute in multi-agent protocols

Cyclophosphamide Species-Specific Metabolism

Dogs and cats are actually much more efficient at converting CP to the active 4-OHCP than humans and it is almost entirely attributable to higher affinity for the parent drug CP.
**Vinca Alkaloids (Vincristine and Vinblastine)**

**Basic Pharmacology**

**Mechanism of Action**
- Binds to tubulin preventing microtubule assembly
- Cells accumulate in G2/M
- Cells die by apoptosis or mitotic catastrophe

**Indications**
- Multicentric lymphoma (single agent or in combination)
- Epitheliotropic lymphoma
- Mast cell tumors
- Histiocytic sarcoma
- Cats
- Mast cell tumors
- Lymphoproliferative disorders

**Conventional Dosing**
- Vincristine
  - 0.5 - 0.75 mg/m² iv bolus weekly in dogs and cats
- Vinblastine
  - 2.5 mg/m² every 1-2 weeks
  - 3.0 - 3.5 mg/m² every 2-3 weeks

**Vincristine/Vinblastine Specific Considerations**
- ABC's Mutant Dogs
  - More susceptible to VCR-induced myelosuppression

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**Lomustine (CCNU)**

**Basic Pharmacology**

**Mechanism of Action**
- Lomustine (CCNU) is highly lipid soluble and spontaneously decomposes to a reactive center capable of DNA binding, DNA-DNA and DNA protein crosslinks
- CCNU undergoes extensive hepatic metabolism but is orally active due to active metabolites being formed

**Indications**
- Lymphoma in dogs (CHOP)
- Transmissible Venereal Tumors
- Mast Cell Tumors
- Lymphoma in dogs
- Histiocytic sarcoma
- Epitheliotropic lymphoma

**Use in Animals**

**Conventional Dosing**
- Lomustine
  - 60 mg/m² IV bolus weekly in dogs and cats
  - 24 - 36 mg/m² every 2 weeks in dogs
  - 24 - 36 mg/m² every 2 weeks in cats

**Lomustine Specific Considerations**
- Hepatic toxicity may be reduced by coadministration with denmarin
  - Denmarin increases glutathione levels and is an antioxidant and "liver tonic"
- PK of lomustine is poorly defined due to extensive metabolism and the presence of active metabolites

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**Carboplatin**

**Basic Pharmacology**

**Mechanism of Action**
- Metabolized primarily through reactions with water and elimination by binding to plasma and tissue proteins
- Measured primarily as total Pt and it is important to differentiate "bound" and "free" fractions in the plasma
- Primarily eliminated in the urine with 65% of the total dose recovered in the urine 24 hours after administration – Thus correlation between AUC and GFR
- Myelosuppression is the primary toxicity

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**Vincra Alkaloid Indications and Dosing**

**Conventional Dosing**
- Lomustine
  - 60 mg/m² IV bolus weekly in dogs and cats
  - 24 - 36 mg/m² every 2 weeks in dogs
  - 24 - 36 mg/m² every 2 weeks in cats
**Carboplatin Use in Animals**

Pharmacokinetic and Phase I Evaluation of Carboplatin in Dogs

Carboplatin was tested in a Phase I study in dogs with spontaneous tumors. PK and toxicity were performed to determine a safe dose. Drug was given as a 30 min infusion as a dose escalation study.

**Carboplatin Indications and Dosing**

**Conventional Dosing**

- **Dogs**: 300 mg/m² IV over 10-15 minutes q3w
- **Cats**: 240 mg/m² IV over 10 minutes q3w

**Carboplatin Specific Considerations**

- Strong correlations exist with carboplatin exposure and renal function such that dosing can be based on measures of renal function
- Individualized dosing means that carboplatin can be used in cats with overt renal disease using GFR-based dose modifications

**Toceranib (Palladia®)**

**Basic Pharmacology**

- Blocks activation of wild type and mutant Kit
- Orally available
- Nearly identical to the human drug sunitinib both in terms of chemistry and activity
- First "molecularly targeted agent" approved for use in veterinary oncology

**Mechanism of Action**

- Tyrosine kinase inhibitors
- Have activity against a number of receptor tyrosine kinases including VEGFR, FGF, PDGFR and Kit
- Compete with ATP at the ATP binding site to block tyrosine kinase activity
- Tumor cells that are addicted to the activity of these RTKs should be especially sensitive to blocking these signaling pathways

- Blocks activation of wild-type and mutant Kit
- Nearly identical to the human drug sunitinib both in terms of chemistry and activity
- First "molecularly targeted agent" approved for use in veterinary oncology

**Toceranib Indications and Dosing**

**Indications**

- **Dogs**:
  - Approved for mast cell tumors
  - Anal sac adenocarcinoma
  - Gastrointestinal stromal tumors
  - Thyroid carcinoma
  - Nasal adenocarcinoma
- **Cats**:
  - Most cell

**Conventional Dosing**

- **Dogs**: 3.25 mg/kg PO q48h
  - 2.5 – 2.75 mg/kg Mon, Wed, Fri
- **Cats**: 2.7 mg/kg Mon, Wed, Fri

**Toceranib Studies in Animals**

Alternate-day dosing resulted in less toxicity and target serum concentrations could be achieved for 50% of the dosing interval at 2.5 – 3.25 mg/kg EOD Trough Levels

**The End!**

Feel free to contact me for copies of my powerpoint at: Daniel.Gustafson@colostate.edu