
Recommendation 1: If the study collected data on harms and benefits, the title or abstract should so state.

*Title with benefits and harms:*
Safety and efficacy of a genetic vaccine targeting telomerase plus chemotherapy for the therapy of canine B-cell lymphoma. (Gavazza et al, 2013)

*Title with primary harms aim:*
Gum arabic-coated radioactive nanoparticles cause no short-term local or systemic toxicity in the clinically relevant canine model of prostate cancer. (Axiak-Bechtel et al, 2014)

*Abstract with benefits and harms:*
No significant difference in remission or survival time could be demonstrated between treatment groups. Incidence of hematologic and gastrointestinal tract toxicoses did not differ between treatment groups, with the exception that vomiting was more common among dogs treated with the multiagent protocol. (Simon et al, 2008)

*Abstract with primary harms aim:*
The drug was discontinued in 22 dogs because of toxicoses. Toxicoses occurred in 13 dogs with gastrointestinal toxicosis, 4 dogs with thrombocytopenia, 3 dogs with increased alanine transaminase, 1 dog with neutropenia, and 1 dog with progressive azotemia. Eight dogs developed some degree of azotemia during treatment. Hepatotoxicosis was observed at a median of 265 days in 11 dogs. Thrombocytopenia was identified at a median of 432 days of administration. (Tripp et al, 2011)

Recommendation 2: If the trial addresses both harms and benefits, the introduction should so state.

*Introduction with benefits and harms:*
…the aim of the present study was to evaluate the observed response rate and toxicity associated with the use of vinorelbine alone for the treatment of dogs with measurable MCT. (Grant et al, 2008)
Introduction with primary harms aim:
The objectives of the following Phase I study were (1) to determine the maximum tolerated dose (MTD), safety, and toxicoses of elsamitrucin when administered weekly to tumor-bearing dogs that had failed or declined standard therapy and (2) to evaluate the incidence and severity of adverse events (AEs) related to elsamitrucin administration. (Fiocchi et al, 2011)

Recommendation 3: List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs. unexpected events, reference to standardized and validated definitions, and description of new definitions).

List with definitions and grading (new system):
During these examinations, the wound was evaluated for presence of blood, swelling, depigmentation, and for the recovery of the eyelid structure. A scoring system was established to grade these features. For the features blood, swelling, and depigmentation, grades 0, 1, and 2 were used for ‘not’, ‘mildly’, and ‘clearly’ present. (Romkes et al, 2013)

List with definitions and grading (referral to established system):
…gastrointestinal toxicities, cardiotoxicity, skin reactions, stomatitis and myelosuppression were monitored and graded according to the Veterinary Cooperative Oncology Group (VCOG) toxicity grading system. (Teske et al, 2011)

Recommendation 4: Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent).

Active data collection for laboratory-derived events:
For each cat, CBCs were performed weekly for a minimum of 4 weeks after treatment with carboplatin (day 0). If the neutrophil or platelet count was not within reference limits by the fourth week, weekly CBCs were continued until the values were within reference limits. (Bailey et al, 2009)

Active data collection for clinical events:
Owners were sent home with a notebook containing daily evaluation forms to be completed the week after doxorubicin (Fig 1). The forms asked owners to grade their pet’s clinical signs on a visual analog scale. Marks on the scale corresponded to the VCOG-CTCAE, ranging from 0 (none) to 4 (life threatening) for factors including vomiting, diarrhea, nausea, appetite, and activity level. (Rau et al, 2010)
Timing of ascertainment:
Standardized ophthalmic examinations were performed on IMRT-treated dogs prior to RT, at completion of therapy, 2 and 4 weeks post therapy, and then every 3 months thereafter. (Lawrence et al, 2010)

Harms-related stopping rules:
If a grade 4 adverse event occurred, the dog was discontinued from study. (London et al, 2009)

Dogs were removed from the study if a significant toxicity occurred that precluded continuation of doxorubicin administration at the same dose. (Withers et al, 2014)

Recommendation 5: Describe plans for presenting and analyzing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses).

Coding (rules used to group similar or related events):
High liver enzyme activities...were defined as any increase in alanine aminotransferase > 69 IU/L, alkaline phosphatase > 157 IU/L, or \( \gamma \)-glutamyltransferase > 16 IU/L. (McMillan et al, 2011)

Handling of attributable vs. non-attributable events:
Adverse events [included] any undesirable event, expected or not, occurring in a dog during the study, whether considered as having a causal relation to study treatment or not. (Vail et al, 2012)

Handling of recurrent events:
Hematologic toxic effects were summarized by summary statistics, and hematologic nadirs were reported as a minimum value for each dog and each treatment. Non-hematologic toxic effects were summarized as a maximum grade for a specific type of event for each treatment. (Flory et al, 2008)

... the number of toxicity episodes at each dose level and for each organ system were recorded separately for each dog. (Zenker et al, 2010)

Analysis:
To determine biochemical tolerability as a function of cumulative zoledronate treatment cycles, serum parameters (creatinine, blood urea nitrogen [BUN], calcium, phosphorus, and potassium) representative of kidney function were evaluated with linear regression analysis. (Fan et al, 2008)

...the Mann–Whitney test was used to evaluate the gastrointestinal, haematologic and psychological effects of zoledronic acid on dogs with metastatic bone disease.
biochemical toxicities between carboplatin alone versus carboplatin and rosiglitazone combined. (Allstadt Frazier et al, 2012)

Haematological toxic effects were summarized by summary statistics, and haematological nadirs were reported using the lowest value for each dog. (Rassnick et al, 2010)

**Recommendation 6: Describe for each arm the participant withdrawals that are due to harms and the experience with the allocated treatment.**

*Harm-related withdrawals and deaths:*  
No dogs died or were euthanized due to treatment-related toxicoses, but four of these five dogs discontinued chemotherapy because of the adverse effects. Additionally, one dog discontinued treatment due to toxicity (as assessed by its owner) despite the fact that this dog did not require hospitalization. (Dervisis et al, 2011)

Five dogs were withdrawn from the study because of adverse effects (one from group Y and four from group N). (Mason et al, 2014)

Another adverse event that was noted in 1 dog was uroabdomen that was observed 2 days after MMC treatment…It was not known if the uroabdomen was caused by tumor-related bladder damage, catheter injury, or other causes. The dog’s owner requested euthanasia of the dog and did not elect for further medical care or for necropsy after euthanasia. (Abbo et al, 2010)

*Treatment exposure:*  
Thirty-two dogs (16 in each treatment group) completed their prescribed six-dose treatment protocol. The remaining 18 dogs stopped treatment early due to progressive disease after five doses (6 dogs), four doses (2 dogs), three doses (1 dog), two doses (7 dogs) or one dose (2 dogs). (Skorupski et al, 2013)

**Recommendation 7: Provide the denominators for analyses of harms.**

*Harms assessed in all enrolled animals:*  
Safety was assessed in all dogs in both the treatment arms. (Marconato et al, 2014)

*Harms only assessed in some enrolled animals:*  
Acute toxicity effects could be evaluated in all cats… Late toxicity effects could be evaluated in 10 cats that survived longer than 6 months. (Poirier et al, 20130)
Recommendation 8: Present the absolute risk of each adverse event (specifying type, grade, and seriousness per arm), and present appropriate metrics for recurrent events, continuous variables and scale variables, whenever pertinent.

*Absolute risk of adverse event by type and grade (narrative):*
Twenty-three of 24 (96%) dogs experienced gastrointestinal adverse effects, including inappetence, vomiting, diarrhea, or some combination of these. Sixteen (66.6%) dogs vomited during their hospitalization (1 grade-1, 13 grade-2, 2 grade-3). Twenty-three of 24 (96%) dogs also developed diarrhea (4 grade-1, 8 grade-2, 10 grade-3, 1 grade-4). Inappetence developed in 23/24 (96%) dogs for a variable amount of time (8 grade-2, 9 grade-3, 6 grade-4). Five (21%) dogs also received partial parenteral nutrition. Twenty-three of 24 (96%) dogs lost weight (median, 10%; range, 4.1–21.2%). (Willcox et al, 2012)

*Absolute risk of adverse event by type and grade (table), with recurrent events:*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Anemia</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>No toxicity</td>
<td>Seven cats</td>
<td>Seven cats</td>
<td>Seven cats</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0</td>
<td>One cat (cat 2)</td>
<td>One cat (cat 1)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0</td>
<td>One cat (cat 1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>One cat (cat 4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>One cat (cat 4)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(Williams et al, 2010)
Absolute risk of adverse events by type and grade (table), without recurrent events:

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Group I (n = 8)</th>
<th>Group II (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Hyporexia/anorexia</td>
<td>n = 3</td>
<td>n = 4</td>
</tr>
<tr>
<td>Lethargy</td>
<td>n = 4</td>
<td>n = 1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>n = 3</td>
<td>n = 0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>n = 1</td>
<td>n = 0</td>
</tr>
<tr>
<td>Fever</td>
<td>n = 0</td>
<td>n = 1</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>n = 0</td>
<td>n = 8</td>
</tr>
<tr>
<td>Alopecia</td>
<td>n = 5</td>
<td>n = 3</td>
</tr>
<tr>
<td>Weight loss</td>
<td>n = 3</td>
<td>n = 5</td>
</tr>
</tbody>
</table>

(Lucas et al, 2013)

Recommendation 9: Describe any subgroup analyses and exploratory analyses for harms.

Sub-group analysis for harms:
Finally, the Mann–Whitney test was used to evaluate the gastrointestinal, haematologic and biochemical toxicities between carboplatin alone versus carboplatin and rosiglitazone combined. (Allstadt Frazier et al, 2012)

Exploratory analysis for harms:
The effect of body weight, considered as a continuous variable, on presence or absence of adverse effects on the bone marrow or gastrointestinal tract was studied with univariate logistic regression analysis… Body weight had no effect on adverse bone marrow (odds ratio, 1.03; 95% confidence interval, 0.93 to 1.14; \( P = 0.55 \)) or gastrointestinal tract signs (odds ratio, 1.00; 95% confidence interval, 0.92 to 1.09; \( P = 0.98 \)). (Marconato et al, 2011)

Recommendation 10: Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information on harms.

Limitations due to surveillance methods:
In the current study, only 3 dogs developed hypertension, 2 of which were classified as grade 3. This clinical toxicity may have been underreported as blood pressure was measured only in animals showing signs consistent with systemic hypertension or illness. (Bernabe et al, 2013)
Limitations due to surveillance duration:
Finally, only 6 of 21 dogs received imatinib mesylate for longer than 14 days and follow-up examination is lacking in this study. It is thus possible that longer duration of treatment would have resulted in the development of hepatotoxicity in a subset of dogs. (Isotani et al, 2008)

Generalizability:
Another potential weakness is the exclusion of dogs with mast cell tumours. This was a conscious effort due to the previously stated inherent propensity for dogs with mast cell tumours to have clinical or subclinical gastric ulceration secondary to tumour degranulation. Excluding dogs with mast cell tumours has the advantage of ensuring that observed gastrointestinal AEs would be attributable to treatment and not disease. Care should be exercised if this combination is subsequently applied in dogs with macroscopic mast cell disease. (Pan et al, 2014)

References


Copyright, American Veterinary Medical Association, 2016

Available at: http://avmajournals.avma.org/toc/javma/249/9


Copyright, American Veterinary Medical Association, 2016

Available at: http://avmajournals.avma.org/toc/javma/249/9


Copyright, American Veterinary Medical Association, 2016

Available at: http://avmajournals.avma.org/toc/javma/249/9


Copyright, American Veterinary Medical Association, 2016
