Osteosarcoma: treatment beyond surgery

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Providing the best quality care and service for the patient, the client, and the referring veterinarian.

Osteosarcoma (OSA)

- Aggressive destruction of bone
  - Attendant pain
  - Structural damage
- High potential for metastasis
  - 90% of dogs with OSA have microscopic metastasis at the time of presentation
  - 7% have macroscopic evidence of metastasis at diagnosis
Osteosarcoma (OSA)

- Treatment of the primary bone lesion
  - Amputation
  - Limb-sparing surgery
  - Radiation therapy
    - Palliative
    - Stereotactic
  - Bisphosphonate therapy
    - Pamidronate, Zolendronate
  - Radioisotope
    - Samarium-153
Osteosarcoma (OSA)

- Treatment of the primary bone lesion
  - Median survival time with amputation alone is only 4 to 5 months
  - Less than 10% of dogs alive at 1 year
  - Surgery alone is considered to be palliative

Chemotherapy

- Addition of chemotherapy to surgery and/or radiotherapy increases the life expectancy
  - Median survival time increases from 103–175 days to 262–450 days
  - 1-year survival rates with chemotherapy range from 31–48%
  - 2-year survival rates with chemotherapy range from 10–26%
Cisplatin chemotherapy

- Cisplatin increases the median survival time to 10–12 months, with approximately 20% of dogs living longer than 2 years
  - Median survival times are between 180 and 400 days
  - 1-year survival rates are between 30% and 62%
  - 2-year survival rates are between 7 and 21%

Cisplatin chemotherapy

- Cisplatin is nephrotoxic and strongly stimulates the emetic response
  - Administered with vigorous intravenous diuresis with sodium chloride to prevent renal damage
  - Antiemetics should be administered to prevent vomiting
Carboplatin chemotherapy

- Median survival of about 11 months
  - 35.4% of the dogs alive one year after surgery
- Carboplatin is not nephrotoxic and usually does not cause gastrointestinal signs

Doxorubicin (Adriamycin) chemotherapy

- 30 mg/m² given every 3 weeks resulted in poor survival times
- 30 mg/m² given every 2 weeks for 5 treatments resulted in similar survival times as with cisplatin
- Side effects compared to Carboplatin
  - Cardiotoxic
  - Gastroenteritis
  - Extravasation risk
Combination chemotherapy

- **Cisplatin + Doxorubicin**
  - Median survival comparable to cisplatin chemotherapy alone

- **Carboplatin + Doxorubicin**
  - Combinations yield median survival times of approximately 8 to 11 months

- **Carboplatin + Gemcitabine**
  - Median survival time of approximately 9 months

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Combination chemotherapy

- **Carboplatin + Piroxicam/Cyclophosphamide**
- +/- **Toceranib (Palladia®)**
  - **Rationale**: Metronomic therapy with piroxicam and cyclophosphamide is felt to inhibit tumor angiogenesis and regulatory T cells
  - Palladia is also thought to have immunomodulatory effects against tumors largely by suppressing myeloid-derived suppressor cells and tumor-associated macrophages
**Carboplatin + Piroxicam/Cyclophosphamide +/- Toceranib (Palladia®)**

- 126 dogs enrolled at 21 institutions
- All dogs received amputation and carboplatin chemotherapy (4 treatments)
- Dogs were randomized to receive piroxicam/cyclophosphamide with or without toceranib (n = 63 each) after completing chemotherapy

**Outcome**

- Thirty-two dogs (25%) developed progressive disease prior to beginning oral therapy
- More toceranib-treated dogs (n = 8) were removed from the study for therapy-associated adverse events compared to control dogs (n = 1)
- 1-year survival rates of 38.4% and 34.9% for toceranib-treated dogs and control dogs, respectively
  - Comparable to the 35.4% 1-year survival rate reported for carboplatin alone.
Chemotherapy: Alternative delivery

- Intra-arterial injection
- Subcutaneous injection
- Liposome-encapsulated chemotherapy
  - STEALTH liposomes as nanocarriers slowly release drug in the acidic environment of the neoplastic tissue
  - Enable higher concentration of the drug in tumor tissue

Chemotherapy: Timing

- Neoadjuvant chemotherapy is routinely administered to human OSA patients to determine histologic response
  - Good histologic response is <10% viable tumor in the resected tumor
- Pre-operative carboplatin has not been shown to improve the disease-free interval or overall survival for dogs treated with amputation
Chemotherapy: Timing

- Postoperative period is a compromise between allowing time for surgical recovery and not allowing time for micrometastases to grow
- Chemotherapy initiated at either 2 days or 10 days after amputation
  - No difference in survival
  - Increased toxicity was seen in the dogs treated 2 days after surgery

Chemotherapy: Timing

- Chemotherapy after the development of pulmonary metastases has been shown to be ineffective in prolonging survival times
- One retrospective study showed that approximately 48% of dogs with metastatic OSA experienced clinical benefit (primarily consisting of stable disease) following toceranib (Palladia®) therapy
Future treatment possibilities

There appears to be a "ceiling" beyond which present conventional chemotherapy does not appear to be able to improve median survival times

- Canine: 45% survival at 1 year
- Human: 70% survival at 5 years

Future treatment possibilities

- Targeted therapies
- Advantages over standard chemotherapeutic approaches using cytotoxic agents
  - Specifically modulate molecules uniquely expressed by cancer cells rather than by all rapidly dividing cells in the body
  - Improved efficacy and better safety profiles
Targeted therapies: TKIs

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- Tyrosine kinase receptors
- Expressed at higher levels in canine osteosarcoma than normal tissues
  - HER2
  - c-MET
  - c-KIT
  - IGF-1R
  - EGFR
  - PDGFR
  - PKC

Targeted therapies: Immunotherapy

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- Coley’s Toxins:
  - Accidental acquisition or intentional inoculation of *Streptococcus pyogenes* could result in regression or delayed recurrence of various cancers
  - A vaccine consisting of killed bacteria, *Streptococcus pyogenes* and *Serratia marcescens*, was efficacious in the treatment of a variety of tumor types, including bone sarcomas
Targeted therapies: Immunotherapy

- Liposome-encapsulated Muramyl Tripeptide phosphatidylethanolamine (L-MTP-PE)
  - Liposomal form of peptidoglycan cell wall of mycobacteria
  - In vivo stimulation of macrophages and monocytes rendering them cytotoxic against tumor cells

- The addition of L-MTP-PE following cisplatin significantly increased median survival time for dogs to 14.4 months compared to other groups treated with surgery, cisplatin and liposomes alone averaging 9.8 months
Targeted therapies: Immunotherapy

- HER2/neu Targeting Vaccine
  - Utilizes the intracellular bacteria *Listeria monocytogenes*
  - Genetically modified to express a tumor associated antigen, Her-2/neu
  - Stimulates an immune response against tumor cells remaining following removal of the primary tumor (limb amputation)

- 18 dogs with appendicular osteosarcoma following amputation and carboplatin chemotherapy
  - 11 of the 18 treated dogs have surpassed the MST of the control group (historical control dogs, 316 days) and 8 were alive as of Dec 2014
  - Adverse events were mild to moderate and primarily consisted of fever, lethargy, and nausea/vomiting
Future treatment possibilities

- Individualized treatment determined by primary tumor cell cultures
- **Case Study:** 7 year old Golden Retriever, osteosarcoma of the left proximal tibia
  - Established and characterized the primary tumor cell culture
  - Predicted the most effective targeted agent
  - Treated the patient successfully for 24 months