

Treatment Of Metastatic Osteosarcoma

Osteosarcoma (OS) is the most common malignant bone tumour in children and teenagers. Osteosarcoma is also the most common bone tumour in dogs, accounting for 90% of all bone tumours in this species. The major complication of OS is the spread (metastasis) of the tumour from the bone to the lungs. In spite of chemotherapy, human patients who develop metastasis have a very poor prognosis with a 5-year survival rate of less than 20%. In dogs, 90% will develop pulmonary metastasis, and in spite of treatment, less than 20% will be alive 2 years after diagnosis. Metastasis thus remains the most significant and untreatable complication of both human and canine OS. It is clear that in order to have any chance of long-term survival, these patients will require treatment with novel and targeted biological therapies.



Using a series of cutting-edge technologies that have allowed us to look at genetic and molecular changes in osteosarcoma tumour cells, participating centres have identified a new molecule called thioredoxin reductase (TrxR), which contributes to OS metastasis. Auranofin is an inhibitor of TrxR. Auranofin is used in humans and in dogs for the treatment of active, progressive, or destructive forms of inflammatory arthritis, such as rheumatoid arthritis. We now have preliminary data in a mouse model of OS showing that auranofin dramatically reduces OS lung metastasis. Therefore, auranofin has clinical potential for the prevention/treatment of both human and canine OS metastasis.

In this study, we are testing auranofin for its ability to inhibit lung metastasis and increase survival in dogs with OS. If successful, this study will result in near-term veterinary and human patient benefit. It will change veterinary practice for the treatment of OS, and pave the way for clinical trials in human patients.

Expected Risks: Auranofin is used to treat some forms of arthritis in humans, dogs and cats. At high doses, auranofin causes some gastrointestinal disturbances (e.g. diarrhoea), but this problem is generally resolved by lowering the dose. This trial will begin with a lower dose (3 mg tablet every 3 days) than the maximum recommended dose in dogs (9 mg daily), so it is expected that side effects will be avoided. Rare side effects of auranofin use can include reduced numbers of platelets, red blood cells or white blood cells. In addition, auranofin may lead to kidney, liver or skin complications. However, these side effects are rare and all dogs will be monitored throughout the trial, and the dose lowered or discontinued if adverse side effects are observed.

Expected Benefits: Auranofin has been tested in a mouse model of OS and was effective at significantly reducing lung metastasis without any side effects. We expect that auranofin will not decrease survival in dogs but that it will reduce metastasis in a similar manner as in mice, and that as a result, it may increase disease-free survival of canine OS patients. In addition, pre-clinical data gathered from this study will be critical for follow-up in human patients, where the potential exists for auranofin to also decrease metastasis and increase survival. Significantly, this trial may lead to new management practice in canine OS patients.

Participating Centres:

- (1) Sarcoma Research Group, The University of Queensland Diamantina Institute, Brisbane, Qld.
- (2) The Australian Animal Cancer Foundation, Brisbane Veterinary Specialist Centre, Brisbane, Qld.
- (3) Department of Orthopaedics, The Wesley Hospital, Brisbane, Qld.
- (4) Department of Oncology, Princess Alexandra Hospital, Brisbane, Qld.
- (5) School of Animal and Veterinary Sciences, The University of Adelaide, SA.
- (6) Victorian Animal Cancer Care, Melbourne, Vic.
- (7) Veterinary Specialist Services, Brisbane, Qld.
- (8) Perth Veterinary Specialists, WA.