Outcome of a Multicentre Clinical Trial of Auranofin Plus Standard of Care in Dogs With Osteosarcoma


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Introduction

Osteosarcoma (OS) is the most common primary bone malignancy in children. Neoadjuvant and adjuvant chemotherapy combined with surgery can deliver cures of almost 70%. However, the major cause of death in OS, is drug resistant metastasis to the lung for which little improvement in survival has been made since the late 1980s. We have identified multiple metastasis drivers1-5 including thioredoxin reductase 2 (TrxR2). TrxR2 is immediately actionable with auranofin. In preclinical models auranofin reduced OS pulmonary metastases4. Auranofin showed synergistic effects with vorinostat and rapamycin on OS viability and apoptosis induction in a recently reported in vitro and murine study6. OS in dogs is histopathologically, transcriptomically and clinically similar to human OS.

Materials and Methods

We performed a single arm multicentre clinical trial of auranofin in combination with standard-of care (amputation + carboplatin) via specialist veterinary oncology clinics in Australia. We used a historical control group (n=26) receiving standard-of-care only. In the treatment group, dogs >15kg received 9mg auranofin q3d PO and dogs <15kg received 6mg q3d. Follow-up occurred over at least a 3-year period and surviving dogs continue on auranofin.

Results

We recruited 40 dogs to the treatment group. Auranofin induced no adverse events. Auranofin + standard-of-care resulted in a significant increase in overall survival with a hazard ratio of .5776299, standard error of .1617391, z = -1.96 and P> |z| = 0.050 and a confidence interval of 3336638 to .9999773. At the time of writing there were six dogs surviving without measurable disease in the treatment group with survival times of between 577 and 1296 days.

Discussion

Auranofin improved overall survival when combined with standard of care therapy. Our data justify a larger Phase II/III trial in dogs as the basis to change OS standard of care management of canine OS. Our data justify a phase I/II trial in human OS patients with drug refractory disease at the time of initial surgery.

References


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