

Targeted Delivery of Doxorubicin-loaded Cockle Shell-derived CaCO₃ Aragonite nanoparticles on Dog Bearing Tumour

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Abstract: The treatment of solid tumour remains a major challenge to oncologist, even when chemotherapy is referred as the best treatment option, with doxorubicin widely used but its application is impaired in its high concentration levels resulting tissue injury. Cockle shell-derived calcium carbonate nanoparticle-loaded with DOX (CS-CaCO₃NP-DOX) has shown a promising potential in the pre-clinical studies. This trial is aimed at exploring the effectiveness of CS-CaCO₃NP-DOX on dogs bearing tumour. A non-blinded open clinic trial of CS-CaCO₃NP-DOX on dogs with solid tumour. The primary and secondary endpoints were evaluated every 3 weeks for 15 weeks. There was not major adverse effect observed with the formulation. Although, partial response and progressive cRECIST response were recorded in the two cases enrolled. This preliminary finding shows that biogenic CS-CaCO₃NP-DOX is potentially effective on treating solid cancer in dog and improves the quality of life of dogs with bearing solid tumour.

Keywords: CS-CaCO₃NP, Doxorubicin, Clinical trial, dog, tumour

INTRODUCTION

Biodegradable nanocarriers owing to their feasible properties have drawn the attention of researchers toward their usage as drug delivery [1]. The current index and predictive claims of cancer worldwide is alarming [2], with chemotherapy choice as the best treatment option, though associated with cytotoxicity. This aforementioned problem has necessitated the search of biogenic nanocarrier for the delivery DOX, thereby ameliorates the off targeted effect. Cockle shell-derived CaCO₃ nanoparticles loaded with Doxorubicin (CS-CaCO₃NP-DOX) has shown promising effect in rat model with significant reduction in tumour growth [1]. Although, several cancer models have been employed in the evaluation of the cancer progression [3], although, not all were sufficient in representing the molecular and structural features of cancers in human. Dogs has high potential in cancer research for efficacy evaluation due to their intact immune system [4], thus provide evidence for proof of concept in cancer targeting [5]. To the best of our knowledge no report has been documented on effectiveness of CS-CaCO₃NP-DOX in dogs bearing tumours. Hence, this trial is aimed at to determine the potential of CS-CaCO₃NP-DOX in dogs bearing spontaneous tumours.

MATERIALS AND METHODS

This study was a non-blinded open clinic, trial of CS-CaCO₃NP-DOX in dogs bearing tumours. The trial was carried out center at the Universiti Veterinary Hospital (UVH), Universiti Putra Malaysia (UPM) with an ethical approval by the Institutional Animal Care and Use Committee, IACUC of UPM and a signed informed client consent form. Dogs were cytologically confirmed of solid tumour or with measurable tumour growth. The dogs were scheduled for CS-CaCO₃NP-DOX 30 mg/m² for 4

treatment cycles at 21 days interval. Tumour staging were conducted before each treatment cycle. However, dogs with neutropenia has their drug delivery delayed in accordance to the guideline of Veterinary Cooperative Oncology Group's common terminology for adverse events (VCOG-CTCAE) [6]. The toxicity was accessed by history review, physical and clinical examination at every visit in accordance to the Canine RECIST (cRECIST v1.1) [6], with necropsy done on dogs that died and tissues samples analysed histopathologically. Data were expressed in percentages. Event-time plot was employed using Kaplan-Meier analysis.

RESULTS AND DISCUSSION

A total of two patients were enrolled in the trial. CASE 1 local (M) 3yrs died with CASE 2 Labrador (F) 6yrs fall out of the trial as owner elected for euthanasia. CASE 1 has soft tissue sarcoma, which, reduces in size 4 weeks after the first dose thus, graded to have partial response (PR) (Figure 3.1 A&B). While CASE 2 has osteosarcoma and was graded progressive stage (PS) which the client opted for euthanasia, due to lung metastasis (Figure 3 C&D). The principle behind encapsulation of drugs is to reduce off targeted effects [7], thereby increase its therapeutic index at targeted tumour site. None of the dogs shows any toxicity sign. This could serve as proof of concepts for it sustained release of therapeutic dose of DOX as earlier shows promising effect on mice [1]. The direct comparison of the outcome with previous study was difficult due to the inability to enroll many dogs bearing tumour that could undergo long term therapy. In a similar trial, only few dogs received the last therapy with many fall out earlier than expected due to bone marrow suppression or delay treatment [8]. Beside, no sign of cardiotoxicity by CS-CaCO₃NP-DOX were observed. However, micro-metastasis to the lung are often reported at the point of the osteosarcoma diagnosis [9], which is mostly attributed to the cause of the fall out or death in most trials study. CS-CaCO₃NP-DOX provided a promising safety window against DOX toxicity in the treatment of dogs bearing tumour, thus it further assessment for anti-tumour potential is warranted.



Fig. 3. (A) CASE 1. Soft tissue sarcoma (B) Radiographic view of the soft tissue mass, (C) CASE 2. Osteosarcoma (D) Radiographic of the osteolytic humerus

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