



Original Article

Nanoemulsion formulation of a novel taxoid DHA-SBT-1214 inhibits prostate cancer stem cell-induced tumor growth



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ABSTRACT

The main aim of this study was to evaluate the therapeutic efficacy of an oil-in-water nanoemulsion formulation encapsulating DHA-SBT-1214, a novel omega-3 fatty acid conjugated taxoid prodrug, against prostate cancer stem cells. Nanoemulsions of DHA-SBT-1214 (NE-DHA-SBT-1214) were prepared and characterized. *In vitro* delivery efficiency and cytotoxicity of NE-DHA-SBT-1214 was compared with solution formulation in PPT2 cells. *In vivo* studies included analysis of comparative efficacy of NE-DHA-SBT-1214 with Abraxane® and placebo nanoemulsions as well as post-treatment alterations in clonogenic and sphere-forming capabilities of the tumor cells. Qualitative intracellular uptake studies of dye encapsulated NEs by confocal imaging showed uptake by both monolayer and spheroid cultured PPT2 cells. Treatment of PPT2 cells with NE DHA-SBT-1214 (1nM–1μM for monolayer culture of cells grown on collagen-coated dishes for 48 h) induced complete cell death, showing higher efficacy as compared to the drug solution. This nanoemulsion (10nM–10μM) also showed toxicity in 3D culture of floating spheroids. Weekly intravenous administration of the NE-DHA-SBT-1214 to NOD/SCID mice bearing subcutaneous PPT2 tumor xenografts led to dramatic suppression of tumor growth compared to Abraxane® and placebo nanoemulsion formulation. Viable cells that survived from this *in vivo* treatment regimen were no longer able to induce floating spheroids and holoclones, whereas control and Abraxane® treated tumor cells induced a large number of both. The results show that NE-DHA-SBT-1214 possesses significant activity against prostate CD133^{high}/CD44⁺^{high} tumor-initiating cells both *in vitro* and *in vivo*.

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Introduction

Therapeutic options for treating cancer, affecting a large population of the United States are still very limited [1]. In contrast to other human cancers, incidence and death rates of prostate cancer (PrCr) have significantly increased in the current decade [2]. More than 70% of PrC patients will face post-treatment recurrence and transition of the disease to an incurable state [3]. Similar to many other cancers, PrCr is also caused by a small population of malignant stem cells known as cancer stem cells (CSCs) or tumor-

initiating cells (TICs), which are responsible for tumor development, metastasis, and resistance to anti-cancer therapies [4]. Numerous studies on many cancer types have demonstrated that the tumorigenic cells expressing common CSC markers, in particular CD133 and CD44, are resistant to conventional anti-cancer drugs and these cells can propagate significantly after therapy [5]. The mechanisms of drug resistance in CSCs are thought to be dependent on several factors including up-regulated expression of drug efflux transporters, the activation of anti-apoptotic signaling pathways, inactivation of apoptotic machinery, a state of quiescence, an enhanced DNA damage response and active repair mechanisms. Current prostate cancer treatments primarily target the bulk neoplastic, fast-growing cancer cells but not the CSCs subpopulation. This could provide the reason for the limited

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