Superparamagnetic iron oxide nanoparticles of Sabizabulin (VERU-111) for pancreatic cancer treatment

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BACKGROUND:
Pancreatic cancer (PanCa) is one of the leading causes of cancer-related mortality in the United States due to very limited therapeutic options. Thus, developing novel therapeutic strategies will help for the management of this disease. We recently identified VERU-111, a novel synthetic molecule which showed potent anti-cancer effect against PanCa *via* targeting clinically important βIII and βIV tubulin isoforms. In this study, we synthesized and characterized its novel nanoformulation (MNP-VERU) and evaluated its therapeutic effects *in vitro* and xenograft mouse model.
Methods: MNPs were prepared by chemical precipitation method and loaded with VERU-111 using diffusion method. This formulation was characterized for particle size, chemical composition, and drug loading efficiency, using various physico-chemical methods (TEM, FT-IR, DSC, TGA, and HPLC). The internalization of MNP-VERU was achieved after 6 hours incubation with MNP-VERU in PanCa cells. To determine therapeutic efficacy of MNP-VERU, we performed various *in vitro* (MTS, wound healing, boyden chamber real-time xCELLigence, and apoptosis assays) and *in vivo* (mouse tumor xenograft) studies using PanCa. Effect of MNP-VERU on various key oncogenic signaling pathways, and miRNAs was evaluated by Western blot, immunohistochemistry (IHC), confocal microscopy, qRT-PCR and *in situ* hybridization (ISH) analyses respectively.
Results: Our novel MNP-VERU formulation provided average size of 110 nm in dynamic light scattering (DLS) and exhibited -8.23 to -11.65 mV zeta potential with an outstanding loading efficiency (94%). Cellular uptake and internalization studies demonstrate that MNP-VERU escape lysosomal degradation, providing efficient endosomal release to cytosol. MNP-VERU showed remarkable anti-cancer potential in various PanCa cells (Panc-1, AsPC-1, HPAF-II, BxPC-3, MiaPaca) and more effectively repressed βIII and βIV tubulin isoforms *via* restoring the expression of miR-200c. MNP-VERU more effectively suppressed AsPC-1 cells derived xenograft tumors in athymic nude mice.
Conclusions: Taken together, our results suggest that MNP-VERU has more anti-cancer potential than free VERU-111 against PanCa. MNP-VERU may reduce the toxicity and improve the bioavailability of free VERU-111 and could be used for the management of PanCa and health disparity.
Keywords: Pancreatic cancer; Sabizabulin;VERU-111; Tubulin inhibitor; MNPs