PTU-101

APOPTOTIC EFFECT OF PEGYLATED-NANOPARTICLES OF CDP BOUND TO MULTITARGETED SIRNA MOLECULES AGAINST BMI1 AND SURVIVIN CONJUGATED WITH MIR-373 (TERMED AS SEVIN-A) WHICH TARGET GASTRIC CANCER STEM CELLS (GCSCS) OVEREXPRESSING CD44 AFTER CIRCUMVENTION OF CHEMO

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Introduction Vinorelbine in advanced gastric Ca and other solid tumours induces potent chemoresistance caused by activation of downstream signalling pathways of antiapoptotic survivin, aurora, etc induction of endopolyploidy, and efflux proteins including MDR1/Pgp, BCRP and MRP2.

Methods After vinorelbine treatment in advanced gastric Ca, we observed potent chemoresistance caused by generation of cancer stem cells which were characterised by overexpression of miR-520c, CD44, BIRC5/survivin (IAP), aurora serine/threonine kinases leading to endopolyploidy, Ras/c-Myc, Nanog, MAP4, MDR1/Pgp, BCRP/ABCG2, MRP2 (cMOAT), Hedgehog signalling pathway components including PTCH1, Gli1, Gli2 and downregulation of BRCA1, p53, PTEN and p21. The vinorelbine-induced chemoresistant (VIC) gastric cancer stem cells (GCSCs) termed as VIC-GCSCs were targeted with pegylated nanoparticles of cyclodextrin containing polycation (CDP) bound to multitargeted siRNA molecules against BMI1, and survivin conjugated with miR-373 targeting CD44. The formulation was termed as SEVIN-A.

Results Post-treatment, we observed induction of D2 apoptotic stage of PCD type 1 in VIC-GCSCs leading to a bystander killing effect after downregulation of the chemoresistant antiapoptotic factors and their downstream signalling pathways, and upregulation of apoptotic tumour suppressor genes and downstream target genes. Treatment with SEVIN-A even induced apoptosis in chemoresistant endopolyploid VIC-GCSCs by downregulating Aurora-B.

Conclusion Treatment with SEVIN-A eradicated vinorelbine induced chemoresistant cancer stem cells (VIC-GCSCs) of advanced gastric Ca.

Competing interests None.

Keywords cancer stem cells, chemoresistance, apoptosis, advanced gastric cancer, drug delivery system.