Development of Miriplatin-loaded Nanoparticles against Non-small Cell Lung Cancer

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SIGNIFICANCE

The lipid-based nano-formulations may serve as a potent delivery system for miriplatin against non-small cell lung cancer (NSCLC).

INTRODUCTION

1. Lung cancer claims the highest mortality and the second-most new cases among all oncological diseases. NSCLC accounts for approximately 85% of all newly diagnosed lung cancers.
2. Although platinum-based drugs are recommended standard first-line chemotherapy for stage IIIB/IV NSCLC, accumulating reports have shown failure of conventional platinum-based regimens due to drug resistance.
3. Miriplatin is a lipophilic anti-cancer drug that has been approved in Japan for transcatheter arterial chemoembolization treatment of hepatocellular carcinoma.
4. Lipid-based nanoparticles such as liposomes, micelles, and solid lipid nanoparticles (SLNs) can encapsulate anti-cancer drugs to improve their water solubility and bioavailability.

HYPOTHESIS

Lipid-based nano formulations of miriplatin would carry appropriate physiochemical properties to improve the anticancer activity of platinum drugs against NSCLC.

METHODS

1. **Preparation of Formulations:** Ultrasmall dots and various SLNs were prepared by film-hydration
2. **Characterization of Formulations:** Sizes and PDI of formulations were measured by Zetasizer. A quantification method of platinum recovery was established using inductively coupled plasma-optical emission spectrometry(ICP-OES). The images by transmission electron microscopy (TEM) displayed the sizes and morphology of formulations.
3. **In-vitro Evaluation of Anti-cancer Activity against NSCLC:** A three-dimensional multicellular spheroid model (3D MCS) of A549-iRFP cells was established. During 7-day treatment, the fluorescent signal was recorded and analyzed by Infrared Imaging System at the 700 nm channel. The cell viability was measured by UV absorbance at 490 nm on microplate reader using 3D viability Assay.

RESULTS

Table. The dots were smaller (~10 nm) and more homogeneous (PDI~0.2), whereas SLNs of different compositions were much larger (~120 nm) and more heterogeneous (PDI~0.4). For miriplatin-loaded SLNs with different compositions, the sizes decreased (from 195.00 nm to 22.81nm) as the percentage of 18:0 PE-PEG increased (from 5% to 40%). The quantification of miriplatin by ICP-OES have shown high platinum recovery (>80%) in both ultrasmall dots and SLNs.

Figure1. The images by TEM displayed their sizes and morphology that were consistent with the size and PDI measurements by Zetasizer.

Figure2. The ultrasmall dots and selected SLNs showed significantly stronger 3D MCS inhibition against 3D MCS than free miriplatin, and similar anti-cancer activity to cisplatin. Miriplatin-loaded SLNs with more PE-PEG had higher anti-cancer activity.

RESULTS(CONTINUED)

Table. Size, PDI and Pt Recovery of Miriplatin-Loaded Formulations (SLNs and dots) with Different Compositions

Lipid Compositions	Drug input (molar%)	Size(nm)	PDI	Pt Recovery
SLN: 95%TP/5%PE-PEG	10%Miriplatin	195.00	0.512	/
SLN: 95%TM/5%PE-PEG	10%Miriplatin	121.30	0.262	/
SLN: 90%TP/10%PE-PEG	10%Miriplatin	106.10	0.343	128.81%
SLN: 90%TM/10%PE-PEG	10%Miriplatin	57.34	0.856	94.78%
SLN: 80%TP/20%PE-PEG	10%Miriplatin	79.31	0.413	99.01%
SLN: 80%TM/20%PE-PEG	10%Miriplatin	131.40	0.217	101.07%
SLN: 60%TP/40%PE-PEG	10%Miriplatin	18.81	0.500	/
SLN: 60%TM/40%PE-PEG	10%Miriplatin	22.81	0.846	/
Micelle: 100%PE-PEG	10%Miriplatin	11.24	0.240	/
Micelle: 100%PE-PEG	20%Miriplatin	11.90	0.247	80.80%
Micelle: 100%PE-PEG	*20%Miriplatin+10% Paclitaxel*	11.71	0.254	77.70%
SLN: 90%TP/10%PE-PEG	20%Miriplatin	86.88	0.261	/
SLN: 90%TM/10%PE-PEG	*20%Miriplatin+10% Paclitaxel*	91.45	0.241	/
SLN: 60%TP/40%PE-PEG	20%Miriplatin	137.40	0.379	99.66%
SLN: 60%TM/40%PE-PEG	20%Miriplatin	158.50	0.135	100.98%
SLN: 60%TP/40%PE-PEG	*20%Miriplatin+10% Paclitaxel*	41.08	0.417	91.76%
SLN: 60%TM/40%PE-PEG	*20%Miriplatin+10% Paclitaxel*	94.55	0.868	57.29%

(TM: trimyristin, TP: tripalmitin, PE-PEG: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)-2000] (ammonium salt))

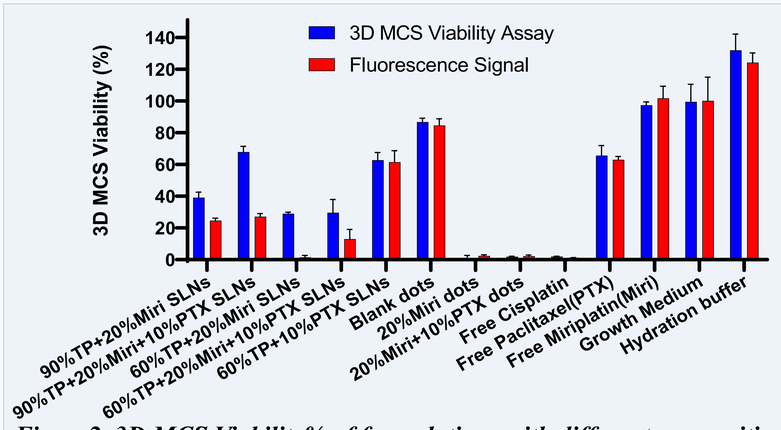

Figure2. 3D MCS Viability% of formulations with different compositions based on 3D Viability Assay and Fluorescence signal (Mean ± S.D, N =3)

(a). ***(b).*** ***(c).***

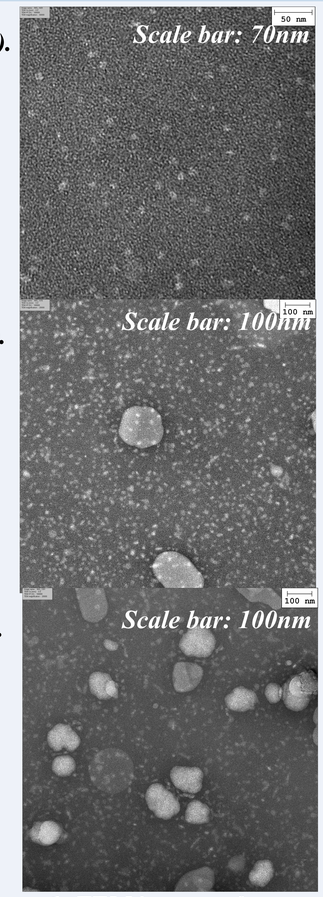

Figure1. TEM images of miriplatin-loaded dots and SLNs. (a) Dots containing 100% PE-PEG + 20% miriplatin. (b) SLNs containing 60% TP/40% PE-PEG + 20% miriplatin. (c) SLNs containing 60% TP/40% PE-PEG + 20% miriplatin+10% paclitaxel.

CONCLUSIONS

The reported lipid-based nano formulations which carried appropriate physiochemical properties represent a promising delivery system for miriplatin against NSCLC.