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The synthesis and cytotoxicity of 64Cu/NOTA-terpyridine platinum conjugate, as a novel theranostic agent

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Objective: Currently, theranostics for both imaging and concomitant chemoradiotherapy is widely used in the treatment of cancerous patients. In this regard, defining the optimal timing between Pt-drugs injection and radiation delivery to the patients is an important issue. Recent advances in the field of nuclear medicine can potentially solve this problem by selective delivery of Pt-based compounds labeled with a positron/Auger-emitting radionuclide to cancer cells. In this study, we designed and validated for the first time a 64Cu-NOTA terpyridine platinum conjugate as a novel Pt-based positron/Auger emitting agent targeting G-quadruplexes DNA structure. This project is aimed to demonstrate that such theranostic agent could give rise to a synergistic effect with a greater selectivity toward cancer cells.

Methodology: The in-vitro cytotoxic and synergistic effects of the conjugate were assessed by Presto-blue assay. The cellular uptake, internalization and efflux of 64Cu-NOTA terpyridine platinum conjugate was measured for colorectal cancer cell (HCT116) as well as a normal fibroblast cell line (GM05757) at 24, 48 and 72 h after initial incubation time.

Results and Discussion: natCu-conjugate showed 3.4, 1.7 and 2.3 times higher cytotoxicity against HCT116 cells relative to GM05757 fibroblast normal cells. However, natCu-conjugate exhibited 9.6, 11.5, 14.1 folds lower cytotoxic effects on HCT116 cells than cisplatin at 24, 48 and 72 h, respectively. The internalization of 64Cu-conjugate in HCT116 cells increased from 15 min (0.04±0.021%) to 24h (18.7±2.8%) and followed by a plateau at 48h (18.6±1.5%), post-administration. The percentages of internalization were significantly higher in HCT116 cancer cells as compared to GM05757 normal cells at 24h, 48h and 72h post-administration (Pvalue<0.001), which is associated with higher cytotoxicity of the conjugate toward HCT116 cells. More importantly, the efflux profile of HCT116 cells showed that considerable amount of 64Cu-conjugate was retained throughout the time course from 15 min (100±7 %) to 72h (48±6%). Additionally, there was a little percentage of the conjugate (<1%) internalized at 4 ℃ and all time points, indicating that passive uptake of the compound is not primarily responsible for internalization. A synergistic (radiosensitizing) effect was measured for the 64Cu-conjugate (5 and 8MBq) at low concentrations (<100μM). Conversely, cell viability (%) started to increase steadily exhibiting an infra-additive (radio-protective) effect at highest concentration (500μM) on the HCT116 cells.

Conclusion: These results support the potential use of 64Cu-labeled terpyridine platinum conjugate as a novel theranostic agent to diagnose and treat cancers.

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