Abstract

The Cytotoxic Effect of ^{64}Cu /NOTA-Terpyridine Platinum Conjugate, as a Novel Chemoradiotherapy Agent [†]

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Abstract: Colorectal cancer is one of the most prevalent cancers worldwide that displays both intrinsic and acquired resistance to platinum-based chemotherapeutic agents (Pt-CAs). To overcome such resistance, new classes of Pt-CAs have been proposed, including terpyridine (TP) compounds that target the G-quadruplex tertiary structure of DNA. Additionally, recent studies indicate a maximum chemoradiation benefit when radiation is administered with Pt-CAs at their highest concentrations in cancer cell DNA. Accordingly, we synthesized a novel chemo-radiotheranostic agent by conjugating a TP moiety with ^{64}Cu (^{64}Cu -NOTA-TP). The in vitro cytotoxic effects, cellular uptake, internalization and efflux of ^{64}Cu -NOTA-TP were measured for colorectal cancer (HCT116) and normal fibroblast (GM05757) cells. Radiolabeling NOTA-TP with ^{64}Cu resulted in 17,530-, 40,083- and 66,000-fold enhancements in its cytotoxicity against HCT116 cells ($\text{EC}_{50} = 0.017 \pm 0.004$, 0.012 ± 0.006 and $0.005 \pm 0.0002 \mu\text{M}$) as compared to ^{64}Cu -NOTA-terpyridine ($\text{EC}_{50} = 298 \pm 2$, 481 ± 25 and $330 \pm 51 \mu\text{M}$) at 24, 48 and 72 h post-administration, respectively. More importantly, the cytotoxicity of the ^{64}Cu -conjugate toward the HCT116 cells was about 3.8-fold higher than that of GM05757 cells at 24 and 72 h. This result was consistent with a 2–3-fold higher internalization of ^{64}Cu -conjugate in HCT116 cells relative to GM05757 cells at similar times. The internalized activity of the ^{64}Cu -conjugate steadily increased from $0.04 \pm 0.02\%$ to $18.7 \pm 2.8\%$ over a 24 h incubation time. Moreover, the efflux kinetics of the ^{64}Cu -conjugate showed that more than 40% of internalized activity was retained by cancer cells over a 24 h period. In conclusion, this work presents a novel chemo-radiotherapeutic agent with considerable potential for targeted cancer treatment combined with radioisotope imaging.

Keywords: chemo-radiotheranostic agent; colorectal cancer; ^{64}Cu -conjugate; cytotoxic effects; G-quadruplex; terpyridine (TP) compounds

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/IECC2021-09220/s1>.

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