J Cancer Res Clin Oncol. 2022 Nov 27.
doi: 10.1007/s00432-022-04385-4. Online ahead of print.

Hyperbaric oxygen enhanced the chemotherapy of mitochondrial targeting molecule IR-780 in bladder cancer

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- PMID: 36436092
- DOI: 10.1007/s00432-022-04385-4

Abstract

Background: Bladder cancer has a high rate of recurrence and drug resistance due to the lack of effective therapies. IR-780 iodide, a near-infrared (NIR) mitochondria-targeting fluorescent agent, has been demonstrated to achieve higher selectivity than other drugs in different tumor types and exhibited tumor-killing effects in some cancers. However, this therapeutic strategy is rarely studied in bladder cancer.

Material and methods: The accumulation of IR-780 in bladder cancer was measured by NIR imaging. Human bladder cell lines (T24, 5637, and TCCSUP) were treated with IR-780 or combined IR-780 and hyperbaric oxygen (HBO). Cell viability, cell apoptosis, cellular ATP production, mitochondrial reactive oxygen species (ROS), and plasma membrane potential were detected. Mitochondrial complex I protein NDUFS1 was measured by western blot. To confirm the anti-tumor efficacy of IR-780 + HBO, mouse bladder cell line (MB49) tumor-bearing mice were established and tumor size and weight were recorded. Besides, cell apoptosis and tumor size were assessed in drug-resistant bladder cancer cells (T24/DDP) and xenografts to evaluate the effect of IR-780 + HBO on drug-resistant bladder cancer.

Results: IR-780 selectively accumulated in bladder cancer (bladder cancer cells, transplanted tumors, and bladder cancer tissue from patients) and could induce cancer cell apoptosis by targeting the mitochondrial complex I protein NDUFS1. The combination with HBO could significantly enhance the anti-tumor effect of IR-780 in

vitro by promoting cancer cell uptake and inducing excessive mitochondrial ROS production, while suppressing tumor growth and recurrence in animal models without causing apparent toxicity. Moreover, this combination antitumor strategy was also demonstrated in drug-resistant bladder cancer cells (T24/DDP) and xenografts.

Conclusion: We identified for the first time a combination of IR-780 and HBO (IR-780 + HBO), which exhibits mitochondria-targeting and therapeutic capabilities, as a novel treatment paradigm for bladder cancer.