Preclinical evaluation of Promitil, a novel nanoparticle formulation of Mitomycin C, in chemoradiotherapy

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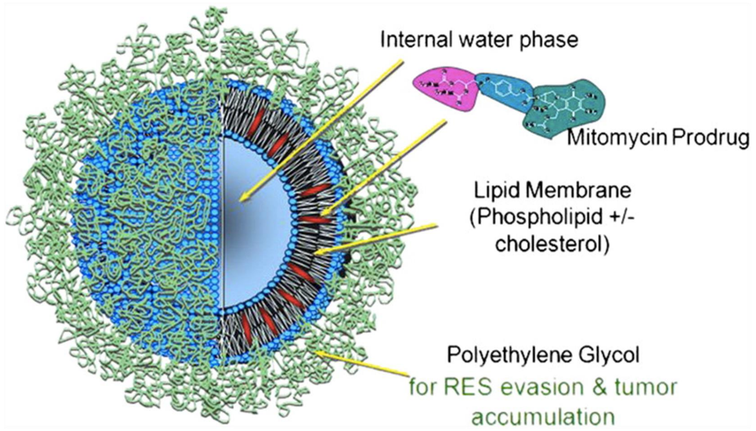
Introduction

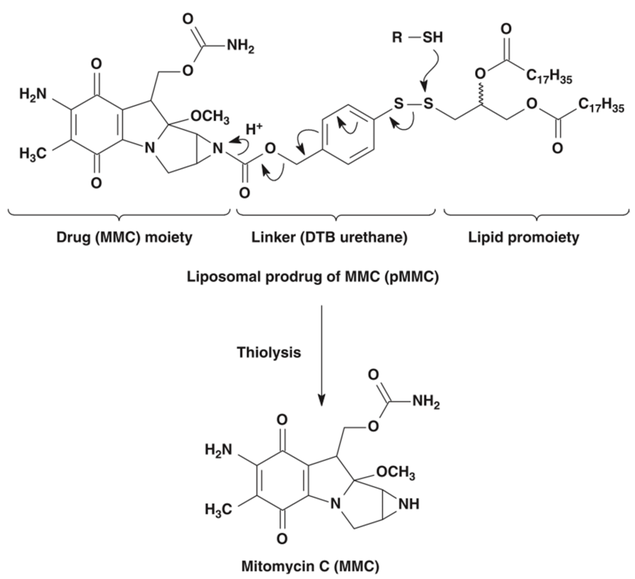


- Lipid-based prodrug of anti-cancer agent Mitomycin C (MMC)
- Developed by LipoMedix Pharmaceutical Inc.
- Currently being studied in a Phase I, dose-escalating, safety study for patients with solid tumor in Israel

Objectives

(1) Evaluate the impact of drug administration and irradiation timing on efficacy
(2) Evaluate the impact of dosage on efficacy in vivo
(3) Evaluate the efficacy and toxicity of Promitil in vivo

Mechanism of Activation

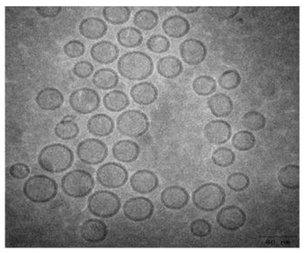


1. Thiolytic environments, such as **tumors environments**
2. **Radiation** ⟶ Cell death ⟶ Apoptotic cells release cytoplasmic contents

⇨ promote thiolysis and release of MMC from the liposome-encapsulated prodrug.

Characterization of Promitil

Cryo-TEM of Promitil



Size: 98.61 ± 0.27 nm by dynamic light scattering

Surface charge:
-13.7 ± 0.49 mV

In Vitro Efficacy of Promitil

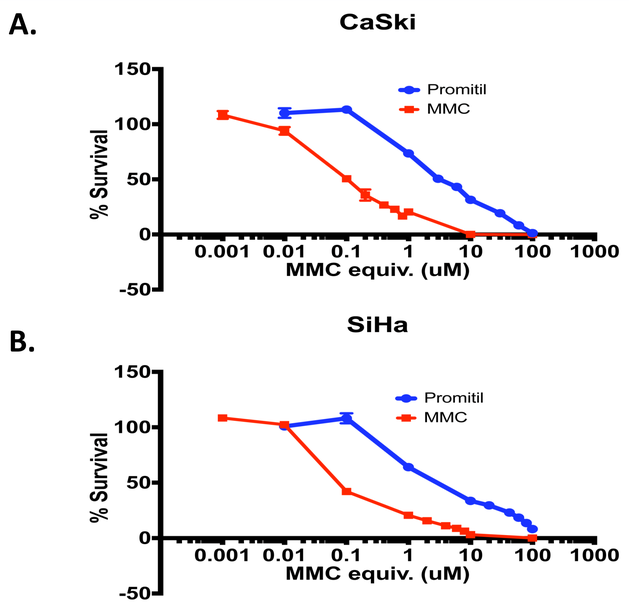


Fig 1. Dose-response assay to measure cytotoxicity of Promitil and MMC in CaSki (A) and SiHa (B). Cells were treated with indicated doses of Promitil and MMC containing an equivalent dose of MMC.

Toxicity

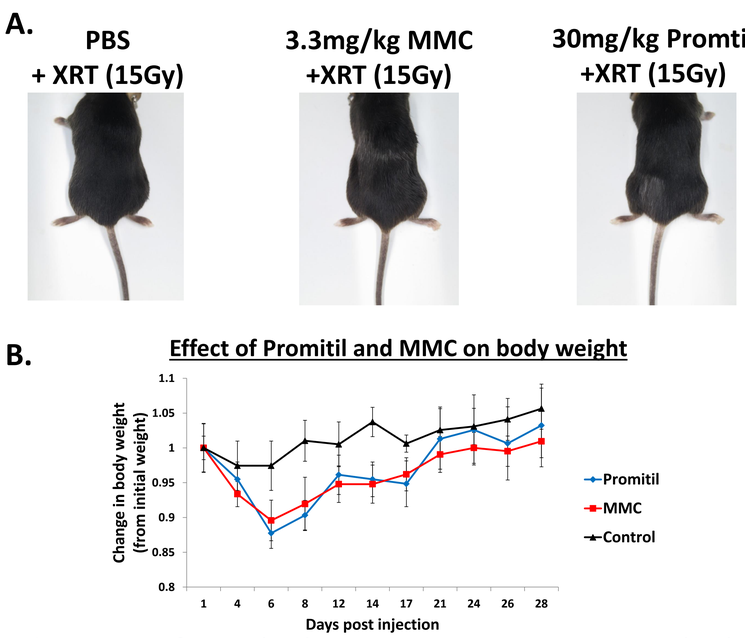


Fig 2. Toxicity of Promitil and MMC in C57 mice. Mice were treated with indicated doses of MMC or Promitil by single tail vein iv injection and followed with 15Gy irradiation. (A) Hair toxicity pictures after 49 days. (B) Changes in body weight were measured.

In Vivo Efficacy of Promitil

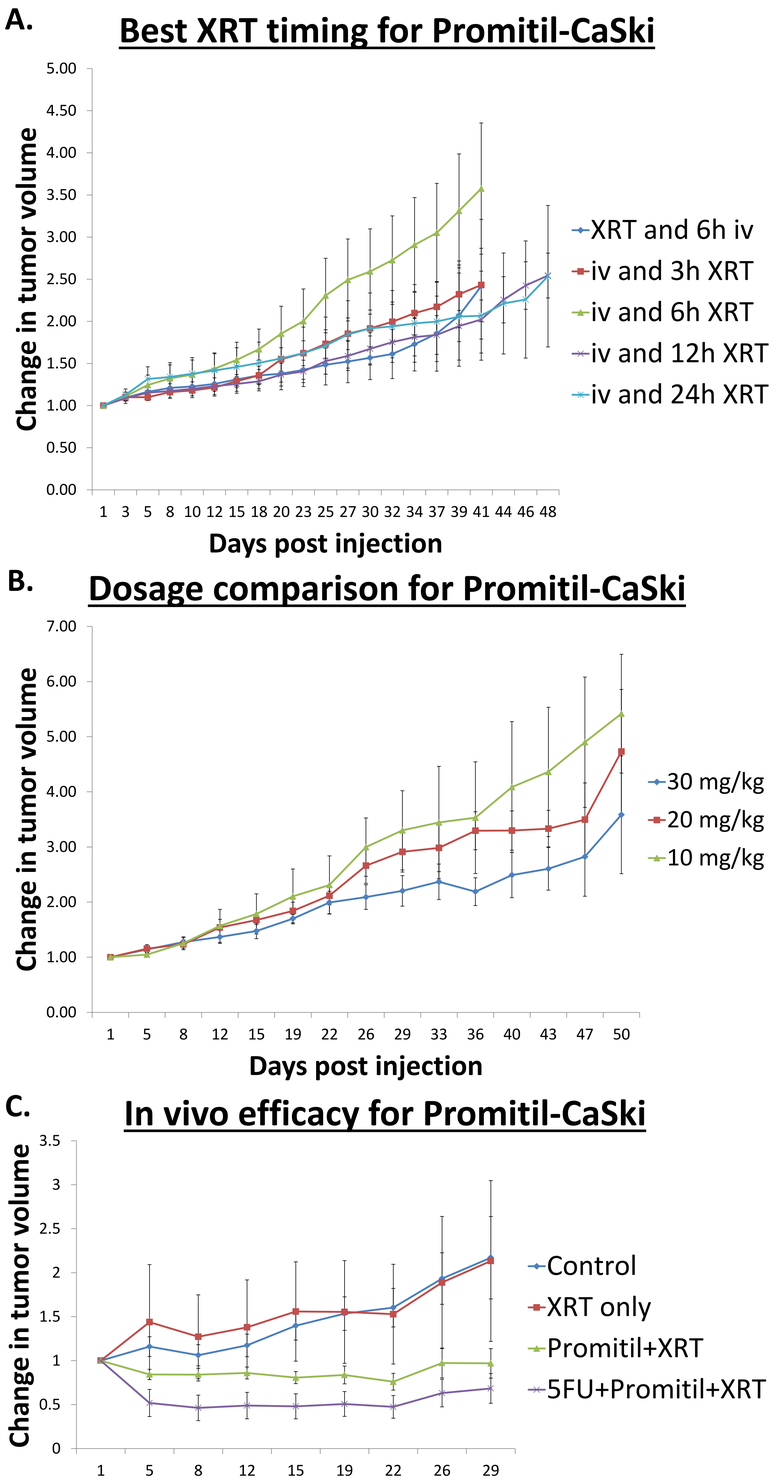


Fig 3. Efficacy of Promitil as a radiosensitizer for squamous cell carcinoma cell line CaSki in vivo. Mice bearing flank tumor xenograft were given Promitil with different timing for radiation therapy (A), or with different doses (B), or comparing with different treatments (C). Changes in tumor volume were measured.

Conclusions

- ❖ Promitil showed less in vitro cytotoxicity than MMC.
- ❖ Mice can tolerate higher doses of Promitil which can improve efficacy.
- ❖ The combination of Promitil and 5-Fluorouracil resulted in the greatest radiosensitization.