Tumor Treating Fields (TTFields) downregulate DNA repair and show efficacy in small cell lung carcinoma preclinical models

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Introduction

- Small cell lung cancer (SCLC) is a highly aggressive malignant neoplasm, accounting for 10-15% of lung cancer cases, characterized by rapid growth, and early metastasis.[1]
- The standard treatment for patients with SCLC is combination chemotherapy with cisplatin or carboplatin plus etoposide, administered together with immunotherapy and concurrent chest radiotherapy.[2]
- Tumor Treating Fields (TTFields) are electric fields that exert physical forces to disrupt cellular processes critical for cancer cell viability and tumor progression, FDA approved for treatment of patients with glioblastoma, pleural mesothelioma, and non-small cell lung carcinoma.[3,4]
- TTFields have been shown to downregulate DNA damage repair pathways and induce immunogenic cell death in various cancer cell types. [3,4]
- The current preclinical study aimed to investigate the efficacy of TTFields together with SCLC standard treatments.

Methods

- **TTFields in vitro:** Human SCLC cells were treated with 150 kHz TTFields: 72 h, 1 V/cm RMS for DMS-53 cells; 120 h, 1.62 V/cm RMS for H196 cells; with or without cisplatin and etoposide (CE).
- **Cell count:** Cells were counted by flow cytometry.
- **Overall effect:** Cells were harvested, re-plated, and grown for 14-28 days. Colonies were stained with crystal violet. Overall effect was calculated by multiplying colonies with respective cell count.
- **Apoptosis:** Cells were stained with FITC-conjugated annexin V (AnnV) and 7-aminoactinomycin D (7AAD) and acquired by flow cytometry.
- **Western blot:** Cell Extracts were prepared using RIPA buffer and subjected to Western blot.
- **DNA damage:** Cells were fixed, permeabilized and stained with anti-γH2AX antibody. Slides were mounted with DAPI nuclear stain, and images collected on a fluorescent microscope.
- **Calreticulin detection:** Cells were stained with anti-CRT antibody and 7-AAD and acquired by flow cytometry.
- **ATP detection:** Cells were incubated with quinacrine dihydrochloride (QA) and 7-AAD and acquired by flow cytometry.
- **HMGB1 detection:** Supernatants were collected and quantified by HTRF assay.
- **TTFields in vivo:** Male C57Bl/6 mice were orthotopically inoculated with 50,000 murine KP3 SCLC cells. 7 days later, TTFields or sham-heat were continuous applied for 11 days. Cisplatin (2mg/kg), etoposide (8mg/kg), and anti-PD-L1 (10mg/kg) were administered i.p. according to the timeline in Figure 4. Tumor volume was examined by magnetic resonance imaging (MRI) at treatment start and end, and tumor volume fold change was calculated. Tumors were dissected and weighed at treatment end.

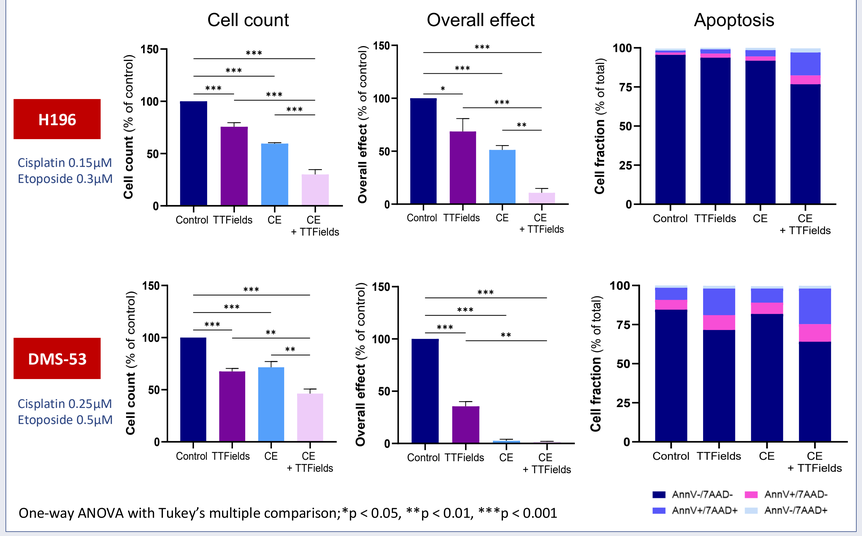
Conclusions

- Our results demonstrate efficacy of TTFields for the treatment of SCLC in preclinical models, and a potential advantage for TTFields concomitant with standard chemotherapy and immunotherapy treatments.
- The enhanced efficacy with TTFields may be attributed to the induction of DNA damage and downregulation of key DNA repair pathways by TTFields and to the induction of immunogenic cell death.

Results

FIGURE 1.

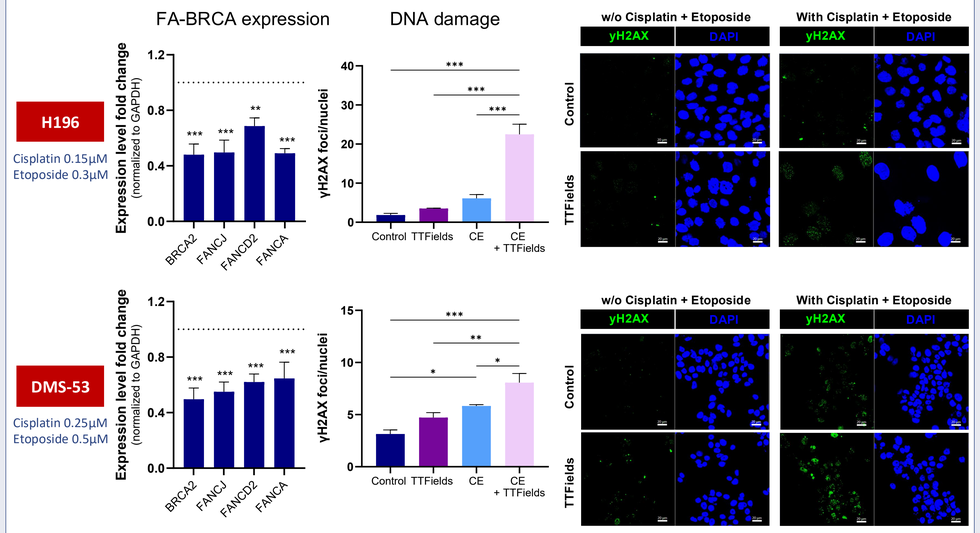
When TTFields were applied with cisplatin and etoposide (CE), greater efficacy was seen relative to TTFields and to the drug combination alone



One-way ANOVA with Tukey's multiple comparison;*p < 0.05, **p < 0.01, ***p < 0.001

FIGURE 2.

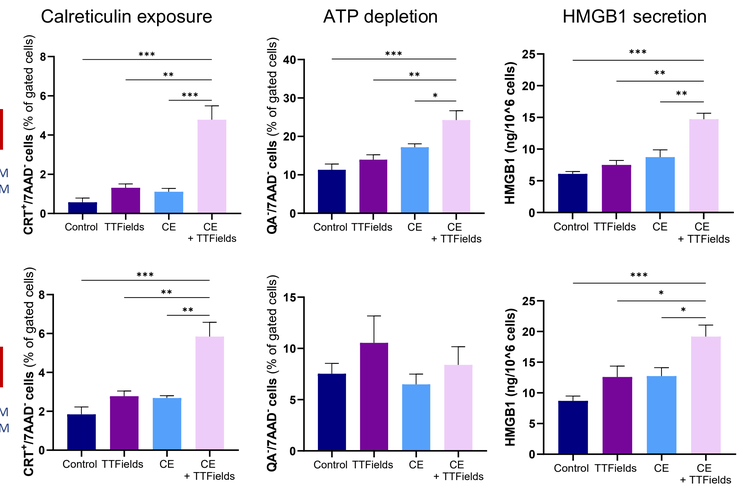
TTFields downregulated expression of proteins from the FA-BRCA DNA repair pathway and, when applied with cisplatin and etoposide (CE) , induced DNA damage in SCLC cells more than each treatment alone



Multiple unpaired t-tests, *p < 0.05, **p < 0.01 , ***p < 0.001

FIGURE 3.

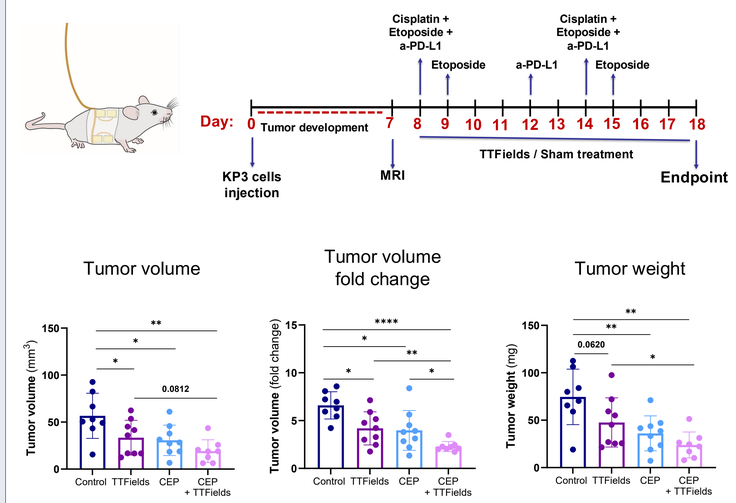
TTFields applied with cisplatin and etoposide (CE) induced immunogenic cell death of the cells, indicative from calreticulin exposure, ATP release, and HMGB1 secretion



One-way ANOVA with Tukey's multiple comparison;*p < 0.05, **p < 0.01, ***p < 0.001

FIGURE 4.

In mice, tumor growth was reduced by TTFields relative to control, with added benefit when applied concomitantly with cisplatin, etoposide, and anti-PD-1 (CEP)



Student's T-test;*p < 0.05 , **p < 0.01, ***p < 0.001 , ****p < 0.0001

References: 1. Siegel RL, et al. (2022*). CA Cancer J Clin.* 72: 7-33. **2.** Petty WJ, Paz-Ares L. (2023). *JAMA Oncol.* 9(3): 419–429. **3.** Karanam NK, Story MD (2021). *Int J Radiat Biol.* 97(8): 1044-1054. **4.** Moser JC, et al. (2022). *Cancer Res.* 82(20): 3650-3658.

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