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Exploring the "sweet spot": in vitro efficacy of tumor treating fields and potential for synergy with cytotoxic therapy in bone and soft tissue sarcomas

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Abstract

Background

Soft tissue and bone sarcomas (STS) are a heterogeneous group of malignancies whose systemic treatment remains constrained by the cumulative toxicity of standard cytotoxic agents, particularly anthracycline-related cardiotoxicity. Tumor Treating Fields (TTFields) are a non-invasive, anti-mitotic therapy that delivers low-intensity, intermediate-frequency alternating electric fields, with growing evidence of activity in several solid tumors. Data on TTFields in sarcoma, and on their potential to interact with cytotoxic and targeted therapy, remain sparse.

Methods

Five sarcoma cell lines (GCT, HT1080, ISO-HAS-B, SJSA-1, SW982) were exposed to 200 kHz TTFields at high (1.62 V/cm) or low (0.76 V/cm) intensity for 72 hours using the inovitro™ system. Cell cycle distribution was assessed by flow cytometry. Doxorubicin, gemcitabine, and pazopanib were each tested concurrently with TTFields, at the field intensity most likely to reveal an added drug effect, and viability was compared with each agent alone.

Results

TTFields alone produced growth inhibition in all five cell lines at high intensity (43–90% reduction relative to control), with reduced and more variable inhibition at low intensity. Cell cycle analysis showed an increased sub-G1 (apoptotic) fraction after TTFields exposure. At high intensity, TTFields alone reduced viability so substantially that concurrent gemcitabine added no detectable further effect. At low intensity, concurrent doxorubicin reduced viability beyond either agent alone in SW982 (an additive-appearing pattern) and SJSA-1 (a pattern more suggestive of synergy) cells, and concurrent high-intensity TTFields enhanced pazopanib activity in ISO-HAS-B cells.

Conclusions

TTFields show variable but consistent monotherapy activity across sarcoma subtypes in vitro, and field intensity determines whether a concurrent cytotoxic or targeted-therapy effect can be detected experimentally. These exploratory findings suggest TTFields may lower the drug concentration needed for comparable sarcoma cell kill in some subtypes, a relationship that warrants formal synergy analysis and in vivo confirmation before clinical translation.

Background

The management of advanced bone and soft tissue sarcoma (STS) remains a considerable oncological challenge. Surgical resection can be curative in localized disease, but metastatic or unresectable STS relies on systemic chemotherapy, most commonly doxorubicin-based regimens. Doxorubicin carries a cumulative, dose-dependent, and largely irreversible risk of cardiotoxicity, which caps lifetime dosing and limits how long an otherwise effective therapy can be continued [1]. Gemcitabine, frequently paired with docetaxel as a first-line or salvage option in selected STS subtypes such as leiomyosarcoma, was evaluated head-to-head against doxorubicin in the GeDDiS trial and did not demonstrate superior efficacy, but remains part of the therapeutic armamentarium [2]. Targeted agents such as pazopanib, a multi-targeted tyrosine kinase inhibitor active against VEGFR, PDGFR and KIT, have also shown activity in non-adipocytic STS in the PALETTE trial, though with their own toxicity profile [3]. There remains a need for adjunctive modalities that could enhance tumor control while allowing lower cumulative doses of these agents.

Tumor Treating Fields (TTFields) are a non-invasive, anti-mitotic therapy delivering continuous, low-intensity (1–3 V/cm), intermediate-frequency (100–500 kHz) alternating electric fields to a tumor-bearing region via transducer arrays. TTFields are approved for use in glioblastoma, based on the phase 3 EF-14 trial demonstrating a survival benefit when added to maintenance temozolomide [4], and in metastatic non-small-cell lung cancer following progression on platinum-based therapy, based on the phase 3 LUNAR trial [5], with an additional approved indication in malignant pleural mesothelioma. Pivotal trial data in locally advanced pancreatic adenocarcinoma (PANOVA-3) [6] and brain metastases from non-small-cell lung cancer (METIS) [7] are under regulatory review. Mechanistically, TTFields exert dielectrophoretic forces on polar intracellular structures, disrupting microtubule polymerization during metaphase and septin localization during cytokinesis, which leads to mitotic catastrophe [8, 9]. TTFields have also been reported to trigger AMPK-dependent autophagy as a stress response [10] and immunogenic cell death that can enhance the activity of anti-PD-1 therapy in preclinical models [11, 12].

Despite this growing evidence base in other solid tumors, data on TTFields in sarcoma are sparse. We hypothesized that sarcoma cell lines of different histological subtypes would show a range of sensitivities to TTFields, and that the cellular stress induced by TTFields might, under the right conditions, sensitize sarcoma cells to concurrently applied cytotoxic and targeted therapy. Here we characterize the in vitro response of five sarcoma cell lines to TTFields at two field intensities and explore, in a hypothesis-generating manner, how field intensity affects the ability to detect interactions with doxorubicin, gemcitabine, and pazopanib.

Methods

Cell lines

Five human sarcoma cell lines obtained from ATCC were used: GCT (giant cell tumor of bone), HT1080 (fibrosarcoma), ISO-HAS-B (angiosarcoma), SJSA-1 (osteosarcoma), and SW982 (synovial sarcoma).

Cells were cultured in standard media supplemented with 10% FBS and antibiotics at 37°C in a humidified incubator.

TTFields application

TTFields were generated using the inovitro™ system (Novocure, Haifa, Israel). Cells were plated (20,000–30,000 cells/well, according to individual growth rates) onto 22 mm round cover glasses. After 24 hours of attachment, cover glasses were transferred to ceramic dishes integrated with transducer arrays. Generator frequency was set to 200 kHz. Because TTFields generate heat, high-intensity fields (1.62 V/cm RMS) were delivered in an incubator set to 18°C and low-intensity fields (0.76 V/cm RMS) in an incubator set to 30°C, so that cell temperature was maintained at 37°C in both conditions; dish temperature was monitored throughout. Control cells without TTFields were maintained at 37°C. At the end of treatment, cells were collected by trypsinization, resuspended in 100 µL PBS, and counted using a Bio-Rad TC20 cell counter with trypan blue exclusion. For cell cycle analysis, cells were fixed, stained, and analyzed by flow cytometry (BD Accuri C6).

Pharmacological treatments

Doxorubicin (0.96–120 nM), gemcitabine, and pazopanib (0.1–50 µM) were added to culture media immediately prior to TTFields initiation. Doxorubicin and gemcitabine combination assays were run over 3 days; pazopanib combination assays were run over 5 days to accommodate its slower, cytostatic mechanism of action.

Statistical analysis

All experiments were performed in triplicate wells (with additional independent replicates as noted in figure legends). Data are presented as mean ± SEM, normalized to untreated control. Pairwise comparisons between TTFields-treated and control groups were performed using two-tailed Student's t-test. A p-value <0.05 was considered statistically significant.

Results

Sarcoma cell lines show a range of sensitivity to TTFields monotherapy

Five sarcoma cell lines representing distinct histological subtypes — GCT (giant cell tumor of bone), HT1080 (fibrosarcoma), ISO-HAS-B (angiosarcoma), SJSA-1 (osteosarcoma) and SW982 (synovial sarcoma) — were exposed to 200 kHz TTFields for 72 hours using the inovitro™ system. The 200 kHz frequency was selected based on prior frequency-optimization work across a range of cancer cell lines showing maximal growth inhibition in this range [13]. Treatment was delivered at two field intensities, high (1.62 V/cm RMS) and low (0.76 V/cm RMS), with incubator temperature adjusted to maintain cells at 37°C despite field-associated heating (see Methods).

At 1.62 V/cm, TTFields reduced cell numbers relative to control in all five lines (Figure 1A), with the magnitude of inhibition ranging from approximately 43% (ISO-HAS-B) to over 90% (HT1080; $p<0.000001$). SJSA-1 also showed a marked reduction (~71%; $p=0.000007$), while GCT and SW982 showed intermediate reductions of approximately 51% and 57%, respectively ($p<0.05$ for both).

When field intensity was reduced to 0.76 V/cm, the overall pattern of inhibition was preserved but attenuated across lines (Figure 1B). HT1080 remained the most affected (~80% inhibition), and SJSA-1 and SW982 showed an intermediate response (~25% and ~41% inhibition, respectively; $p<0.01$), while GCT and ISO-HAS-B showed no statistically significant difference from control ($p=0.79$ and $p=0.74$). These data indicate that the degree of TTFields-induced growth inhibition in sarcoma cell lines depends on both histological subtype and field intensity, although only two intensities were tested and a discrete activation threshold was not formally established.

Consistent with the mitotic mechanism reported for TTFields in other cancer types, flow cytometric cell cycle analysis after 72 hours of 1.62 V/cm TTFields showed an increased sub-G1 fraction, indicative of apoptotic or fragmented cells, across all five lines relative to control, most notably in HT1080 (0.7% to 9.8%) and ISO-HAS-B (5.5% to 12.6%) (Figure 2). This is compatible with, though not direct proof of, TTFields-induced mitotic catastrophe leading to cell death in this sarcoma panel.

High-intensity TTFields limits the ability to detect chemotherapeutic interactions

To explore whether TTFields could interact with cytotoxic chemotherapy, we co-administered gemcitabine — chosen as a representative cytotoxic given its use alongside docetaxel in selected STS subtypes [2] — together with high-intensity TTFields (1.62 V/cm) in HT1080, SW982 and ISO-HAS-B cells. In all three lines, TTFields alone reduced cell numbers so substantially that adding gemcitabine across a wide concentration range did not produce a further, statistically distinguishable reduction. We interpreted this as a practical ceiling effect: near-maximal cell kill from the field alone left little room to observe an incremental drug effect. This observation motivated us to repeat drug co-treatment experiments at the lower, 0.76 V/cm field intensity, where TTFields alone leaves more room for an added agent to demonstrate an effect.

Concurrent low-intensity TTFields and doxorubicin reduce cell viability beyond either agent alone

At 0.76 V/cm, concurrent doxorubicin exposure reduced viability beyond TTFields or doxorubicin alone in both SW982 and SJSA-1 cells over a 3-day assay. In SW982 cells (Figure 3A), the TTFields-plus-doxorubicin curve was shifted downward relative to doxorubicin alone across the concentrations tested

(0.96–120 nM); at 4.8 nM, viability was 52% with doxorubicin alone versus 36% with concurrent TTFields, a pattern most consistent with an additive interaction between the two modalities.

In SJSA-1 cells (Figure 3B), the relationship between the curves differed: rather than a uniform downward shift, the TTFields-plus-doxorubicin curve appeared to shift leftward relative to doxorubicin alone, such that lower drug concentrations achieved viability reductions comparable to those reached only at substantially higher doxorubicin concentrations alone. This pattern is visually more suggestive of synergy than the additive-appearing pattern in SW982; however, we did not perform formal combination-index or Bliss-independence analysis to confirm this distinction, and the basis for the apparent difference between the two cell lines is not established by these data. We regard the SJSA-1 finding as hypothesis-generating rather than confirmatory.

Concurrent TTFields enhances pazopanib activity in ISO-HAS-B cells

Because ISO-HAS-B cells showed little response to TTFields alone at 0.76 V/cm, we tested this line at the higher, 1.62 V/cm intensity together with pazopanib over a 5-day assay; exposure time was extended relative to the doxorubicin experiments because pazopanib, as a receptor tyrosine kinase inhibitor, is expected to act through a slower, more cytostatic mechanism, and 5-day exposure is consistent with standard pazopanib dose-response protocols in solid tumor cell lines. TTFields alone reduced viability to approximately 35% of control, and concurrent pazopanib produced further reductions at higher drug concentrations (Figure 4): at 10 μM pazopanib, viability fell from 24% with drug alone to 13% with concurrent TTFields. This result, from a single cell line and a single tyrosine kinase inhibitor, suggests that even sarcoma lines with limited response to TTFields monotherapy may show enhanced drug activity under concurrent field exposure, though replication across additional agents and angiosarcoma models is needed before broader conclusions can be drawn.

Discussion

This study provides an initial in vitro characterization of TTFields activity across a panel of bone and soft tissue sarcoma cell lines and an exploratory look at how field intensity affects the ability to detect interactions with concurrently applied cytotoxic and targeted agents. Two observations stand out. First, TTFields monotherapy produced growth inhibition across all five cell lines tested, though the magnitude varied by subtype and by field intensity, with HT1080 (fibrosarcoma) consistently the most affected and GCT (giant cell tumor) and ISO-HAS-B (angiosarcoma) the least affected at the lower intensity tested. Second, the intensity at which TTFields is delivered appears to influence whether a concurrent cytotoxic effect can be detected at all: at a field intensity that alone produced near-maximal cell kill, gemcitabine could not be shown to add anything further, whereas at a lower intensity, room opened up to detect an effect of concurrently applied doxorubicin.

The clinical implication that motivated this work is the possibility of dose de-escalation. Doxorubicin's cumulative cardiotoxicity is a recognized barrier to prolonged use in STS [1], and if concurrent TTFields can achieve comparable tumor cell kill at lower doxorubicin concentrations in doxorubicin-responsive sarcoma subtypes, this could in principle support strategies to preserve cardiac function while maintaining oncologic benefit. Our SJSA-1 data, showing an apparent leftward shift in the dose-response curve, are the most suggestive of this possibility, though we emphasize that we have not yet performed the formal analyses (e.g., Bliss independence or Chou-Talalay combination index methods) needed to distinguish additive from synergistic interactions, and the SW982 data are more consistent with a simple additive effect. Clarifying this distinction, and identifying what differentiates SJSA-1 from SW982 in this regard, is a priority for follow-up work.

Mechanistically, the disruption of microtubule polymerization and septin localization described for TTFields in other cancer types [8, 9] offers a plausible explanation for the growth inhibition we observed, and our cell cycle data showing an increased sub-G1 (apoptotic) fraction after TTFields exposure are compatible with this mechanism. However, we did not directly confirm mitotic arrest or spindle disruption in these sarcoma lines, nor did we establish a mechanistic link between field intensity and any specific repair or resistance pathway; targeted confirmation, for example via live-cell imaging, would strengthen this interpretation.

Limitations of this study include its restriction to five cell lines, testing of only two field intensities, use of a single representative tyrosine kinase inhibitor, and reliance on short-term (72-hour to 5-day) viability readouts without formal synergy quantification or in vivo confirmation. Future work should extend field-intensity titration, apply formal combination-index analysis, and evaluate whether TTFields sensitizes sarcoma models to immune checkpoint inhibition, consistent with reports of TTFields-induced immunogenic cell death in other tumor types [11, 12]. Window-of-opportunity clinical studies would ultimately be required to test whether these in vitro observations translate to patients.

Conclusions

This study provides in vitro evidence that TTFields are active across a range of bone and soft tissue sarcoma subtypes, and that field intensity determines whether a concurrent effect with cytotoxic or targeted therapy can be detected experimentally. Our data are hypothesis-generating: they support further mechanistic and combination-index studies, and ultimately in vivo and clinical evaluation, of TTFields as an adjunct to systemic sarcoma therapy, particularly as a strategy to reduce cumulative anthracycline exposure.

Abbreviations

AMPK: AMP-activated protein kinase

ATCC: American Type Culture Collection

FBS: Fetal bovine serum

GCT: Giant cell tumor of bone (cell line)

NSCLC: Non-small-cell lung cancer

PBS: Phosphate-buffered saline

PD-1: Programmed cell death protein 1

PDGFR: Platelet-derived growth factor receptor

RMS: Root mean square

SEM: Standard error of the mean

STS: Soft tissue sarcoma (used here for bone and soft tissue sarcoma)

TTFields: Tumor Treating Fields

VEGFR: Vascular endothelial growth factor receptor

Declarations

Ethics approval and consent to participate

Not applicable. This study used only commercially sourced human cancer cell lines (ATCC) and did not involve human participants, human data, or animal experiments requiring ethics committee approval.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Novocure Ltd. provided equipment and consumables used in this study. The authors declare that they have no other competing interests.

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study design, data collection, data analysis or interpretation, or the decision to submit the manuscript for publication.

Authors' contributions

H.H.L. conceived and supervised the study and wrote the manuscript. E.C.H.W. and C.H. performed the TTFields and drug combination experiments. A.T. and G.G.C.W. contributed to data acquisition and figure preparation. T.T., V.Y., G.T. and K.C. contributed to methodology and resources. All authors reviewed, edited, and approved the final manuscript.

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Figures

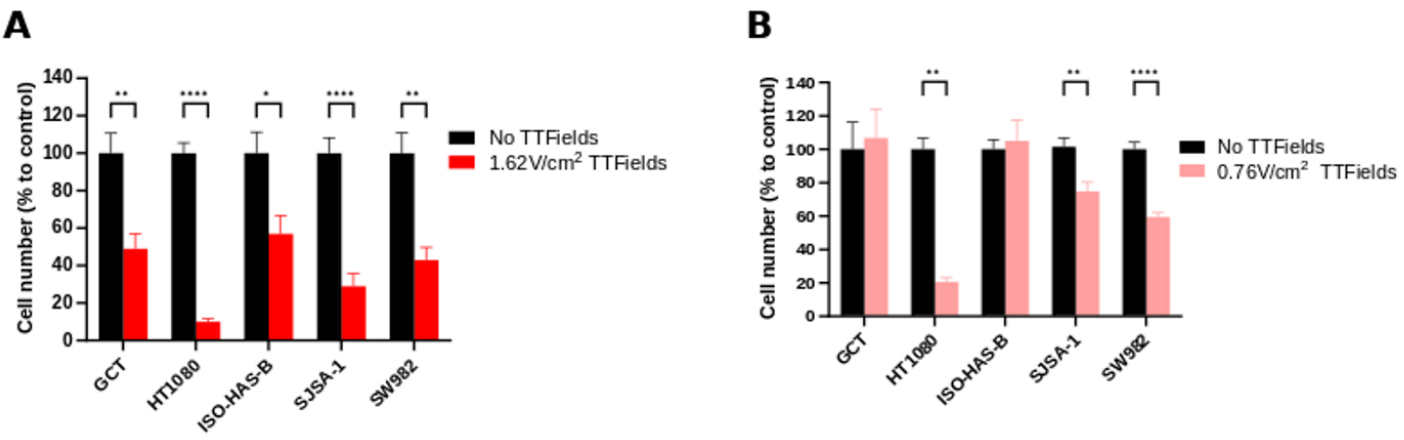


Figure 1

Sarcoma cell lines show a range of sensitivity to TTFields monotherapy. Cell number (% of control) after 72 hours of exposure to (A) high-intensity (1.62 V/cm) or (B) low-intensity (0.76 V/cm) 200 kHz TTFields. Bars show mean ± SEM; *p<0.05, **p<0.01, ****p<0.0001, ns = not significant vs. control (Student's t-test).

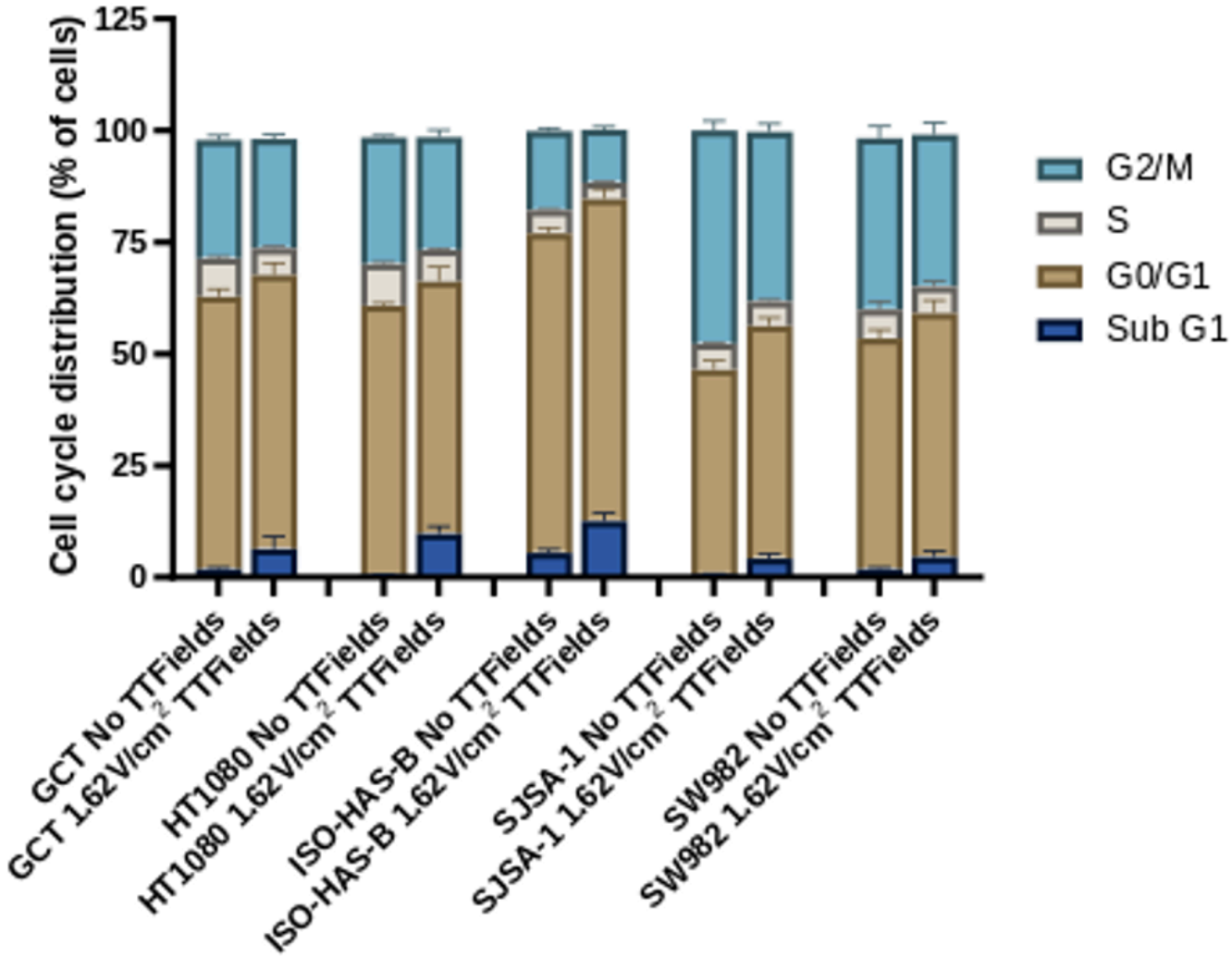


Figure 2

TTFields exposure alters cell cycle distribution. Cell cycle phase distribution (% of cells; Sub-G1, G0/G1, S, G2/M) by flow cytometry in each of the five sarcoma cell lines, with and without 72 hours of 1.62 V/cm TTFields. Bars show mean ± SEM.

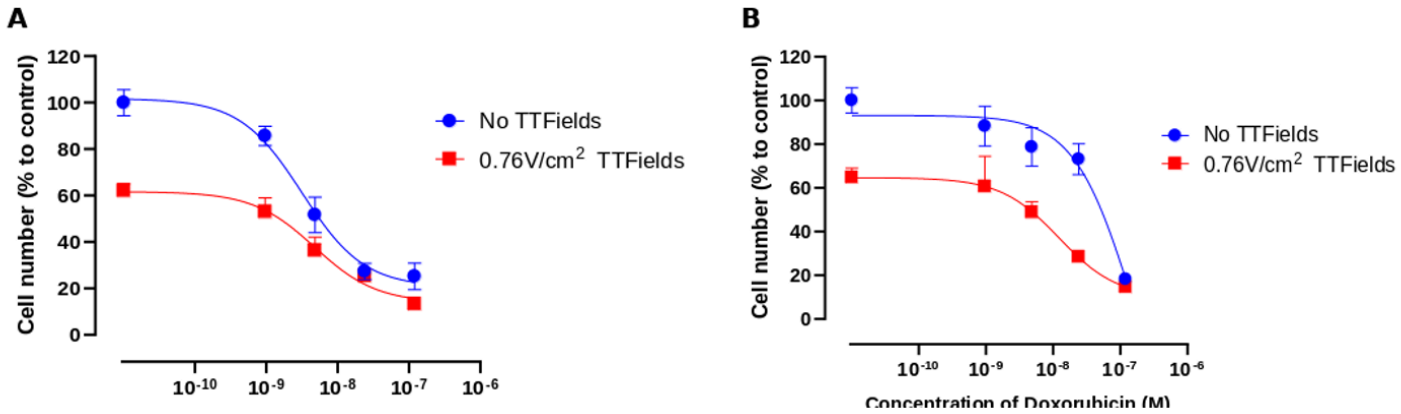


Figure 3

Concurrent low-intensity TTFields lowers the doxorubicin concentration needed for equivalent cell kill. Dose-response of (A) SW982 and (B) SJSA-1 cells to doxorubicin (0.96–120 nM), with and without concurrent 0.76 V/cm TTFields, over a 3-day assay. Data are mean ± SEM, normalized to untreated control.

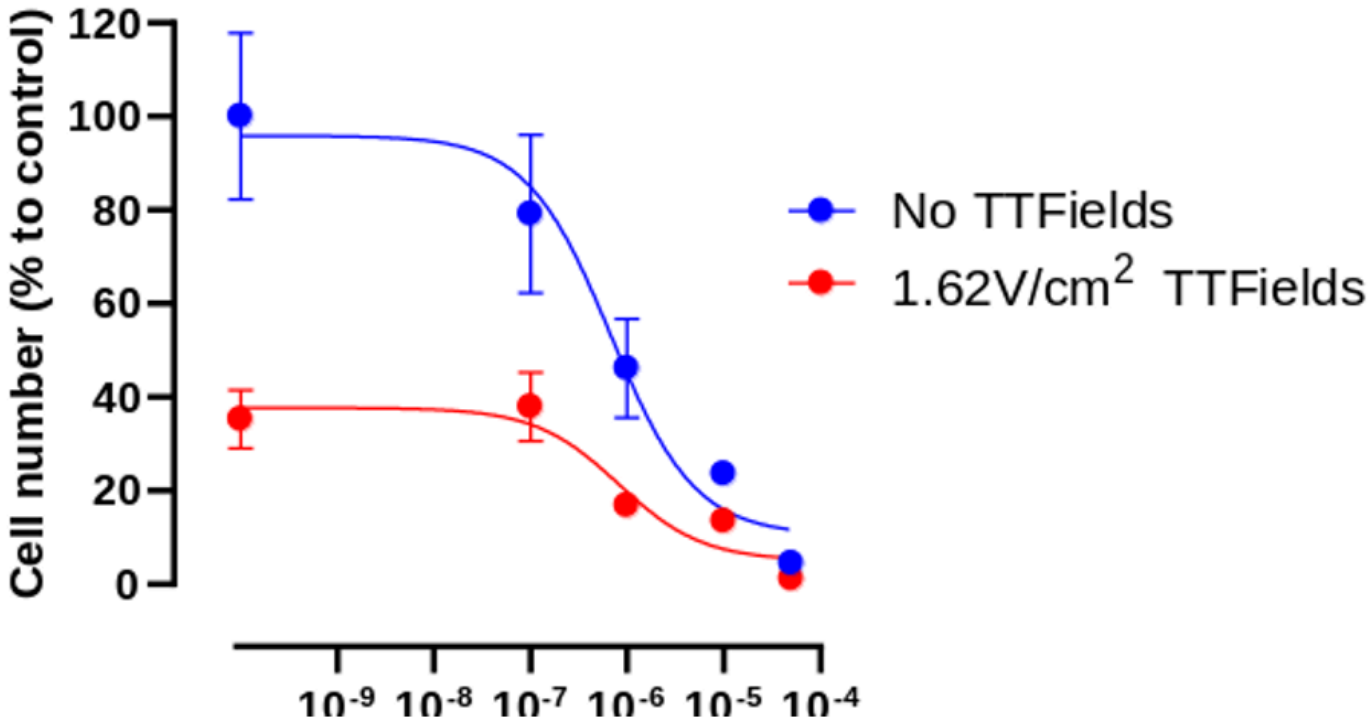


Figure 4

Concurrent high-intensity TTFields enhances pazopanib activity in ISO-HAS-B cells. Dose-response of ISO-HAS-B cells to pazopanib (0.1–50 μM), with and without concurrent 1.62 V/cm TTFields, over a 5-day assay. Data are mean ± SEM, normalized to untreated control.