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Original Article

Dual Targeting Strategy: Colchicine and Paclitaxel Combination Against Prostate Cancer Cells Colchicine-Paclitaxel Synergy in Prostate Cancer

İkili Hedefleme Stratejisi: Kolşisin ve Paklitakselin Prostat Kanseri Hücreleri Üzerindeki Kombine Etkileri

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ABSTRACT

Objective: Prostate cancer is the leading male malignancy. Despite therapeutic advances, drug resistance remains a major obstacle, leading many patients to develop castration-resistant prostate cancer. This study investigates the combined effects of the microtubule-targeting agents colchicine and paclitaxel on DU145 prostate cancer cells.

Methods: Cell viability was evaluated across a range of doses of colchicine and paclitaxel to determine the IC_{50}, IC_{30}, and IC_{10} values for each drug. IC_{10} and IC_{30} doses of the agents and their combinations were selected for subsequent experiments. The effects of the treatments were then analyzed using the MTT assay, the colony formation assay, the *in vitro* scratch assay, and acridine orange/ethidium bromide staining.

Results: Monotherapy with colchicine and paclitaxel indicated dose- and time-dependent cytotoxicity in DU145 cells. Notably, IC_{10} monotherapies had minimal impact on viability, whereas the drug combination produced synergistic inhibition of viability (excess-over-Bliss score: 14.8%), along with marked suppression of colony formation and cell motility ($p<0.0001$). At IC_{30}, the combined treatment nearly abolished colony formation and significantly increased apoptotic and necrotic morphology. These findings reveal that combining sub-therapeutic doses effectively inhibits cell viability, long-term proliferation, and cell motility, where monotherapies are insufficient.

Conclusions: These preliminary findings demonstrate that the colchicine and paclitaxel combination exhibits potent synergistic effects, particularly at low doses (IC_{10}), and effectively suppresses DU145 prostate cancer cell progression. This dual microtubule-targeting approach may overcome the limitations of monotherapy by significantly inhibiting cell motility and clonogenic survival, while enhancing apoptotic and necrotic cell morphology. Our results suggest that low-dose combination strategies may provide high therapeutic efficacy while minimizing systemic toxicity in the management of advanced prostate cancer.

Keywords: Colchicine, paclitaxel, drug combinations, prostate cancer

ÖZ

Amaç: Prostat kanseri, erkeklerde en yaygın görünen malignitedir. Terapötik ilerlemelere rağmen, ilaç direnci önemli bir sorun olmaya devam etmekte ve birçok hastada kastrasyona dirençli prostat kanseri gelişmesine yol açmaktadır. Bu çalışma, mikrotübül hedefleyici ajanlar olan kolşisin ve paklitakselin DU145 prostat kanseri hücreleri üzerindeki kombine etkilerini araştırmayı amaçlamaktadır.

Yöntemler: Kolşisin ve paklitakselin IC_{50}, IC_{30} ve IC_{10} değerlerinin belirlemek için farklı doz aralıklarında hücre canlılığı değerlendirilmiştir. Sonraki deneyler için ilaçların ve kombinasyonlarının IC_{10} ve IC_{30} dozları seçilmiştir. Tedavilerin etkileri, MTT analizi, koloni oluşum deneyi, *in vitro* çizik deneyi ve akridin oranj/etidyum bromür boyama yöntemi kullanılarak incelenmiştir.

Bulgular: Kolşisin ve paklitaksel, DU145 hücrelerinde doza ve zamana bağlı sitotoksisite göstermiştir. Özellikle IC_{10} tekli terapiler düşük etki gösterirken, ilaçların kombinasyonu hücre canlılığı inhibisyonu üzerinde %14,8'lik bir EOB skoru ile anlamlı sinerji sergilemiş; koloni oluşumunu ve hücre hareketliliğini inhibe etmiştir ($p<0.0001$). IC_{30} dozunda, kombine tedavi koloni oluşumunu neredeyse tamamen engellemiş ve apoptotik/nekrotik morfolojiyi önemli ölçüde artırmıştır. Bu bulgular, alt-terapötik dozların kombine halde kullanılmasının, monoterapilerin yetersiz kaldığı durumlarda hücre canlılığını, uzun süreli proliferasyonu ve hücre hareketliliğini etkili bir şekilde inhibe ettiğini ortaya koydu.

Sonuç: Bu sonuçlar, kolşisin ve paklitaksel kombinasyonunun, özellikle düşük dozlarda (IC_{10}) güçlü sinerjik etkiler sergileyerek DU145 prostat kanseri hücresi ilerlemesini etkili bir şekilde baskıladığı kanıtlamıştır. Bu ikili mikrotübül hedefli yaklaşım, hücre hareketliliğini ve klonojenik sağkalımı önemli ölçüde inhibe ederken apoptoz/nekrozu artırarak monoterapinin kısıtlamalarının üstesinden gelebilir. Sonuçlarımız, düşük doz kombinasyon stratejilerinin, ileri evre prostat kanseri yönetiminde sistemik toksisiteyi en aza indirirken yüksek terapötik etkinlik sağlayabileceğini düşündürmektedir.

Anahtar kelimeler: Kolşisin, paklitaksel, ilaç kombinasyonları, prostat kanseri

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INTRODUCTION

Prostate cancer (PC) is the second most commonly diagnosed cancer among men in Türkiye and worldwide, accounting for approximately 18.000-19.000 new cases annually in Türkiye and 1.47 million new cases globally in 2022 according to GLOBOCAN estimates[1]. Although early-stage disease is often responsive to androgen-deprivation therapy, many patients eventually develop castration-resistant prostate cancer (CRPC), characterized by increased proliferation, migration and metastatic potential[2]. Managing this advanced stage PC remains a significant challenge due to resistance to chemotherapy[3], highlighting the need for optimized treatment approaches targeting multiple hallmarks of cancer.

Microtubule-targeting agents (MTAs) are the most clinically effective first-line chemotherapeutics against multiple cancer types. These agents disrupt microtubule (MT) dynamics that play a pivotal role not only for mitotic spindle formation but also for cell motility and polarity by either stabilizing or destabilizing MTs[4]. Paclitaxel (PAC), a well-established MT-stabilizing agent, induces mitotic arrest and apoptosis by blocking MT depolymerization and promoting stability[5]. In contrast, colchicine (CHO) binds to β-tubulin, driving MT depolymerization[6]. Both agents ultimately disrupt cell division and induce apoptosis[5,6].

Combination therapy has become a pivotal strategy for maximizing therapeutic efficacy of drugs while concurrently minimizing toxicity associated with chemotherapy in cancer[7]. The rationale for combining MT-stabilizing and -destabilizing agents lies in their complementary perturbations of MT dynamics. They may produce synergistic cytotoxicity and reduce the clonogenic capacity or motility of cancer cells at more tolerable doses. The present study explores how the combined administration of CHO and PAC affects cell viability, long-term proliferative capacity, motility and cell death-associated morphology in DU145, a CRPC model[8].

MATERIALS and METHODS

Reagents

CHO and PAC were purchased from Sigma-Aldrich. CHO and PAC stock solutions were prepared in EtOH and DMSO, respectively, and were then stored at -20°C. Drug solutions were freshly prepared by dilution in culture media.

Ethics Statement

This study does not involve human participants; therefore, ethical approval was not required.

Cell Culture

DU145 human PC cells were cultured in Dulbecco's Modified Eagle Medium (DMEM, Thermo Scientific) supplemented with 10% (v/v) fetal bovine serum (FBS, Thermo Scientific) and 1% (v/v) penicillin-streptomycin (Pen/Strep, Thermo Scientific). Cells were incubated at 37°C in a humidified incubator with 5% CO_2.

Cell Viability Assay

Cells were seeded at $5x10^3$ cells/well and incubated under standard culture conditions (37°C, 5% CO_2, and high humidity). Cells were then treated with increasing concentrations of CHO (1.25-80 nM) or PAC (1.25-80 nM) for 24 or 48 h. Following incubation with drugs, MTT was introduced into each well, and the cells were incubated for 3 hours. The absorbance was then measured at 570 nm using a microplate reader (Varioskan Lux, Thermo Fisher Scientific).

Colony Formation Assay

The DU145 cells were seeded into 6-well plates and subsequently exposed for 48 hours to IC_{10}, IC_{30}, and a combined IC_{30} dose of CHO and PAC. For colony formation assay, cells were distributed into 6-well plates using a seeding density of 800 cells/well, and maintained for a 10-day period at 37°C with 5% CO_2. Cells were then washed with PBS, fixed with a solution of methanol, acetic acid, and water (1:1:8 v/v), and stained with crystal violet for 20 minutes. Any residual dye was removed with distilled water. Colonies consisting of more than 50 cells were considered viable and subjected to analysis. Colony formation efficiency was calculated as the number of colonies formed divided by the initial number of seeded cells and expressed as a percentage.

In Vitro Scratch Assay

To assess cell motility, $1×10^5$ cells/well were seeded into 24-well plates and incubated overnight at 37°C in a 5% CO_2 incubator. To induce serum deprivation, the growth medium was replaced with fresh medium containing only 0.5% FBS for a 19-hour incubation. Following incubation, a linear scratch (wound) was created across the confluent cell layer using a sterile 200-µl micropipette tip. Cells were then incubated for 48 h in serum-free medium, with or without the addition of CHO, PAC, or their combination, at IC_{10} and IC_{30} doses. Images of scratch area were captured using an inverted

microscope at the indicated time points (Labscope software, Primovert, Zeiss) and quantitatively analyzed using the MRI Wound Healing Tool (RRID:SCR_025260) within ImageJ. To determine the wound area percentage, the final scratched area measured at 48 h was divided by the initial area measured at 0 h.

Acridine orange (AO)/ Ethidium bromide (EB) Staining

AO/EB staining was conducted using a 96-well plate-based protocol with minor modifications[9]. Briefly, cells were seeded at 1×10^4 cells/well in 96-well plates and then treated with IC_{30} doses of CHO, PAC, and their combination. A solution of AO and EB at 100 µg/mL was prepared in PBS, and 16 µl of the dye mixture was added to each well. Fluorescence images were captured using a Zeiss LSM 900 confocal microscope at 10x magnification.

Bliss Independence Model

Drug interactions between CHO and PAC were evaluated using the Bliss independence model[10]. The expected combined inhibitory effect (E_{exp}) on cell viability was calculated using the Bliss equation:

$$E_{exp}=E_{CHO}+E_{PAC}-(E_{CHO} \times E_{PAC})$$

where E_{CHO} and E_{PAC} represent the percentage inhibition induced by each drug alone. To quantify the interaction, the excess-over-Bliss (EOB) score was then calculated as E_{obs} %-E_{exp} %, with positive values indicating synergy ($E_{obs}>E_{exp}$), values close to zero indicating additivity ($E_{obs}=E_{exp}$), and negative values indicating antagonism ($E_{obs}<E_{exp}$).

Statistical Analysis

All statistical analyses were performed using GraphPad Prism 10 software. The normality of the data sets was validated using the Shapiro-Wilk test. A Student's t-test with Welch's correction was used to compare two independent groups. One-way ANOVA followed by Tukey's post-hoc test was employed to perform multiple pairwise comparisons among more than two groups (CTRL, CHO, PAC, and CHO+PAC). Error bars represent the mean ± SEM of a minimum of three independent experiments. Significance is indicated as *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

RESULTS

CHO and PAC Reduced Cell Viability in DU145 Cells in a Dose-Dependent Manner

The cytotoxic effects of CHO and PAC on DU145 cells were assessed at 24 h and 48 h using an MTT assay at concentrations ranging from 1.25 nM to 80 nM. Both CHO- and PAC-treated groups showed a dose-dependent reduction in cell viability over time (Figure 1A-D). The inhibitory concentrations (IC_{50}, IC_{30}, and IC_{10}) of CHO were 51.4 nM, 24 nM, and 2.03 nM, respectively; PAC showed corresponding values of 45.7 nM, 21 nM, and 3.6 nM. At 24 h, CHO caused only a modest decrease in viability at lower doses, whereas at 48 h a more pronounced inhibition was observed, indicating a time-dependent enhancement of cytotoxicity (Figure 1A-B). Similarly, PAC treatment led to a gradual, dose- and time-dependent reduction in viability, with stronger inhibition at 48 h than at 24 h (Figure 1C-D).

CHO and PAC Combination Showed a Synergistic Inhibition in Cell Viability

To investigate the potential synergistic interaction between CHO and PAC in cell viability, the drugs were combined at their respective IC_{10}, IC_{30}, and IC_{50} concentrations, and each combination was evaluated separately. Compared with monotherapies, the combined administration of CHO and PAC at IC_{10}, IC_{30}, and IC_{50} markedly increased cytotoxicity in DU145 cells in a dose-dependent manner (Figure 1E). At higher concentrations (IC_{30} and IC_{50}), both agents reduced cell viability compared with the control, while the combination treatment produced the strongest cytotoxic response ($p<0.0001$). However, CHO alone did not significantly affect cell viability at the IC_{10} concentration, whereas its combination with PAC produced a statistically significant inhibitory effect compared to either the control ($p<0.001$) or PAC alone ($p<0.01$) (Figure 1E). A Bliss independence model was used to determine whether these interactions were synergistic, additive, or antagonistic. The combination of drugs at IC_{10} doses exhibited a 14.8% EOB score, indicating a potential synergistic interaction, while at IC_{30} doses the EOB score was 1.4%, indicating a near-additive interaction (Figure 1E). At IC_{50}, the EOB score was -9.0% indicating an antagonistic tendency at higher concentrations (Figure 1F). Because of the extreme toxicity and antagonistic behavior observed at the IC_{50} doses, subsequent experiments were conducted using the IC_{10} and IC_{30} dose combinations.

Combination Therapy Resulted in a Reduction in Colony-Forming Capacity of the Cells

To assess the combined effects of CHO and PAC on long-term proliferation and clonogenic potential of DU145 cells, a colony formation assay was employed. The findings revealed a marked reduction in clonogenic survival following CHO, PAC, and their combination treatment (Figure 2A). Both monotherapies inhibited colony formation even at low doses (IC_{10}). The IC_{10}

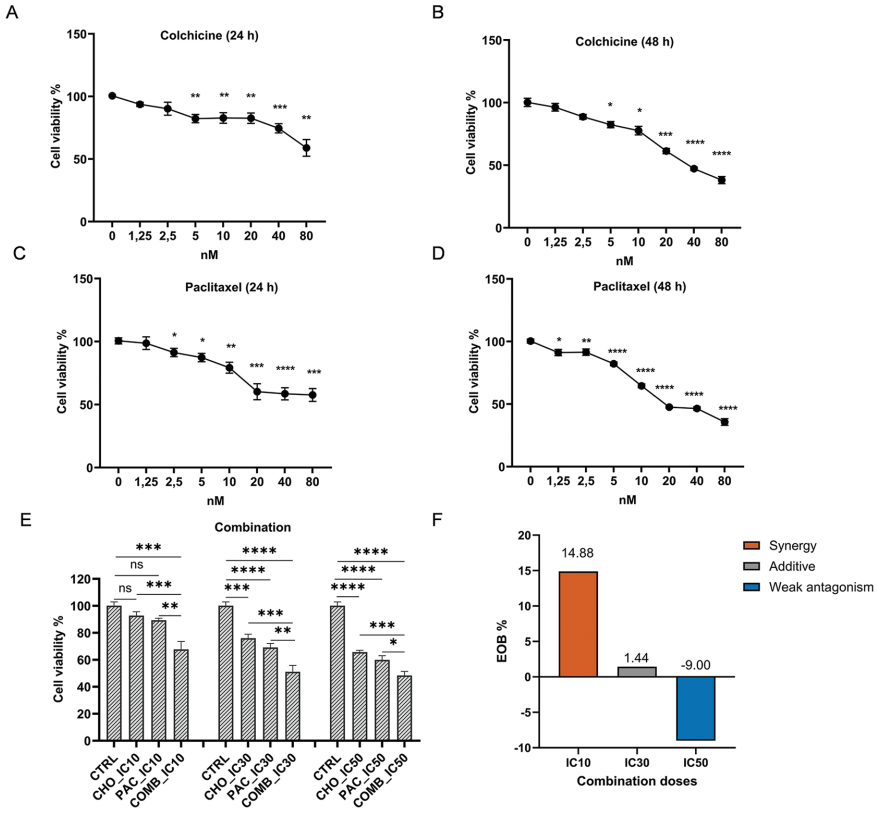


Figure 1. Effects of CHO and PAC co-treatment on DU145 cell viability. Cells were treated with increasing concentrations of CHO (1.25-80 nM) for 24 h (A) and 48 h (B) or paclitaxel (1.25-80 nM) for 24 h (C) and 48 h (D). Comparison of cell viability following individual and combined treatments of CHO and PAC at IC_{10}, IC_{30}, and IC_{50} doses. A Student's t-test with Welch's correction was implemented between single doses. One-way ANOVA with Tukey's post-hoc test was employed between treatment groups (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001). Data are presented as mean ± SEM (E). Excess-over-Bliss (EOB%) analysis illustrating the interaction profile of CHO-PAC combinations. Positive EOB values indicate synergistic interactions, values close to zero indicate additive effects, and negative values are indicative of antagonism (F).

CHO: Colchicine, PAC: Paclitaxel, CTRL: Control, COMB: Combination, EOB: Excess-over-Bliss

combination resulted in stronger inhibition compared with the control group (p<0.0001) and with PAC alone (p<0.01). At IC_{30} concentrations, the combination treatment nearly abolished colony formation. However, at this higher dose, no statistically significant difference was observed between the combination and individual treatments, likely because of the strong inhibitory effects of each drug when administered alone (2B).

Combination Therapy Decreased Cell Motility

To evaluate the effects of the CHO and PAC combination on the motility of DU145 PC cells, an in vitro scratch assay was performed. The untreated control cells exhibited complete wound closure within 48 hours, indicating robust motility (Figure 3A). Notably, monotherapies with CHO or PAC at IC10 doses failed to produce a significant delay in wound closure and were comparable to the control group. However, the combination of these drugs at the IC10 concentration led to a considerable gap in the scratch area (22.6%) compared with either the control or the individual treatments (p<0.0001), resulting in a significant inhibition of motility (Figure 3B). This synergistic inhibitory effect was further enhanced at IC_{30} doses. While monotherapies showed near-complete closure, their combination treatment maintained a markedly wider scratch area (44%) compared to both control and monotherapies (p<0.0001) (Figure 3A-B). These findings demonstrate that even at low doses, where single drugs are ineffective, the combination of CHO and PAC shows a potential additive or synergistic effect in inhibiting the motility of DU145 cells.

Treatment with CHO and PAC Resulted in Apoptotic and Necrotic Cell Morphology

AO/EB dual staining was performed to qualitatively assess the effects of CHO, PAC or their combination at IC_{30} doses on DU145 cell viability. Viable cells exhibited a bright green fluorescence, whereas apoptotic or necrotic cells were characterized by orange or red fluorescence with nuclear fragmentation (Figure 4). Untreated control cells predominantly showed bright green fluorescence with organized cellular morphology. CHO-treated cells exhibited scattered orange fluorescence, indicating the presence of apoptotic-like features and mild cytotoxicity. In PAC-treated cells, an increased proportion of orange-or red-stained cells was observed, suggesting a higher prevalence of morphological changes associated with apoptosis and necrosis (Figure 4B-C). Notably, their combination at IC_{30} doses displayed an increased proportion of orange/red fluorescence compared with the monotherapies, reflecting loss of membrane integrity and morphological changes associated with increased cell death (Figure 4D). These morphological observations were consistent with the additive cytotoxic effects observed in MTT assays.

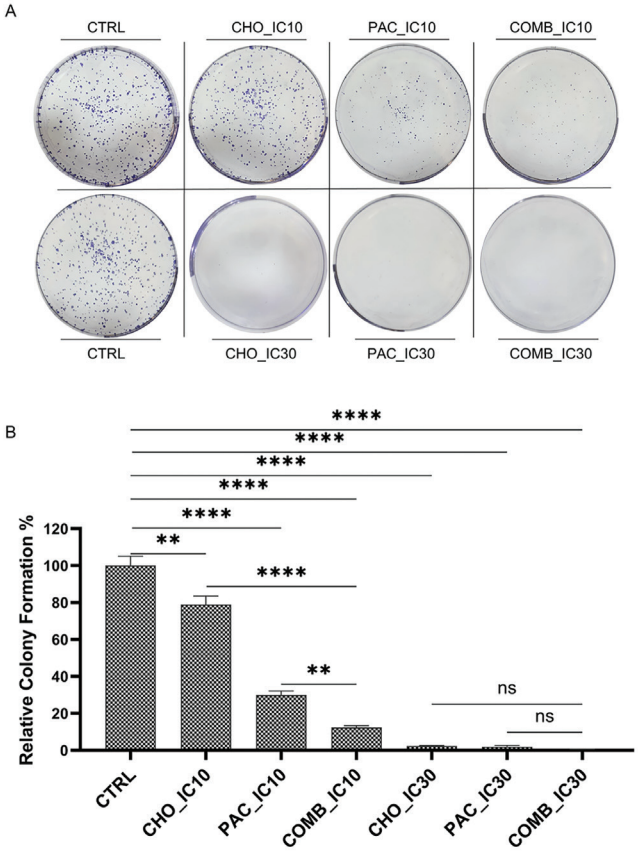


Figure 2. The colony formation assay showing the effects of CHO, PAC, and their combination at IC_{10} and IC_{30} concentrations on DU145 cells (A). Quantification of colony formation expressed as percentage relative to untreated control (B). One-way ANOVA with Tukey's post-hoc test was employed between treatment groups (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001). Data are presented as mean ± SEM.

CHO: Colchicine, PAC: Paclitaxel, CTRL: Control, COMB: Combination

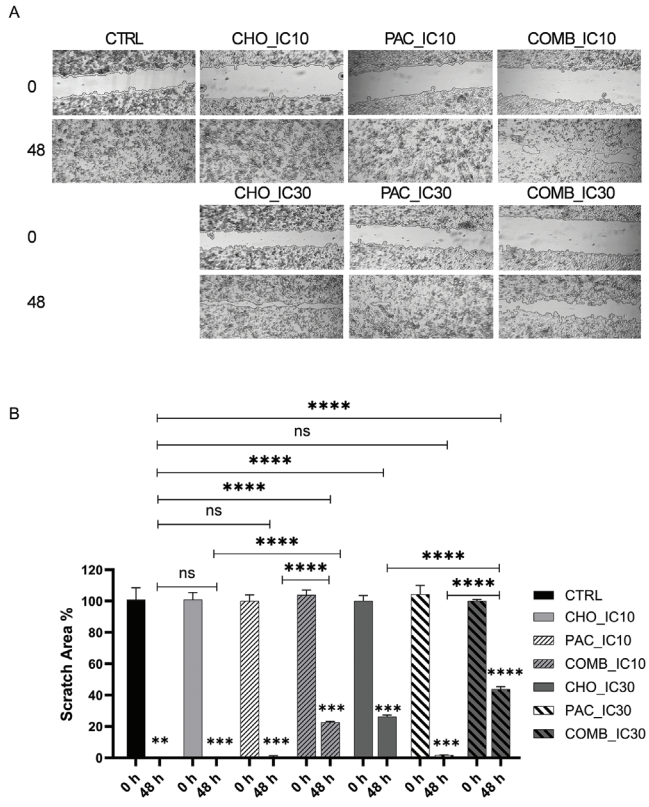


Figure 3. Effects of CHO and PAC co-treatment on DU145 cell motility assessed by a scratch assay. Representative microscopic images showing cell motility of DU145 cells treated with PAC or CHO alone and in combination at their IC_{10} and IC_{30} concentrations for 0 h and 48 h (A). Remaining scratch area at 0 h and 48 h was quantified and expressed as a percentage of the initial scratch area at 0 h for each treatment group (B). A Student's t-test with Welch's correction was implemented between 0h and 48h time point. One-way ANOVA with Tukey's post-hoc test was employed for treatment groups (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001). Data are presented as mean ± SEM.

CHO: Colchicine, PAC: Paclitaxel, CTRL: Control, COMB: Combination, SEM: Standard error of the mean

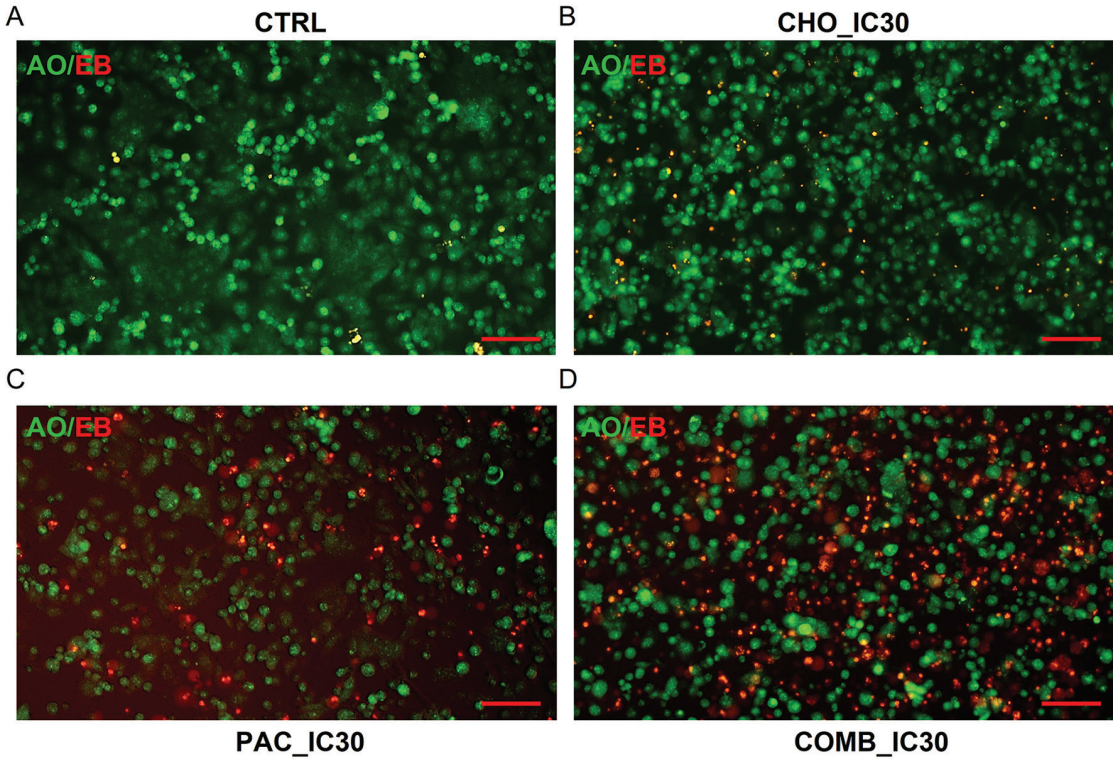


Figure 4. Fluorescence microscopy images of DU145 cells stained with acridine orange/ethidium bromide (AO/EB) following untreated control (A), CHO (B), PAC (C), and their combination treatments (D) at IC_{30} doses. Scale bar: 100 µm. Magnification: 10x.

AO: Acridine orange, EB: Ethidium bromide, CHO: Colchicine, PAC: Paclitaxel, CTRL: Control, COMB: Combination

DISCUSSION

In this study, we demonstrated that MTAs, CHO and PAC, exhibited dose- and time-dependent cytotoxic effects and that their combination resulted in increased inhibition of cell viability, clonogenic potential, and motility by producing a potentially synergistic interaction in aggressive, androgen-independent PC cells.

Both CHO and PAC are well-known agents that bind to tubulin and interfere with MT assembly through distinct effects on tubulin dynamics[11,12]. MTs function as versatile cytoskeletal components, composed of α- and β-tubulin heterodimers, which regulate cellular morphology, motility, and cell division[13]. MTs contribute to the assembly of the mitotic spindle, which is required for chromosome segregation during cell division, and undergo dynamic transitions between polymerization and depolymerization states, maintaining a delicate balance essential for proper cell function. CHO induces MT depolymerization[6], whereas PAC inhibits depolymerization by stabilizing the MT network[5]. Despite these mechanistic differences, both agents ultimately induce mitotic arrest and therefore lead to apoptosis. In this study, each agent reduced cell viability and colony formation independently in a dose-dependent manner, consistent with previous reports in PC cell types[14-20]. Our results revealed dose-dependent changes in drug-drug interactions. The combination at lower doses (IC_{10}) produced significantly greater inhibitory effects than monotherapy, as demonstrated by positive (+14.8%), indicating synergism. However, an antagonistic tendency was observed at the IC_{50} concentration (EOB: -9%), suggesting that the combined interference with MT dynamics is optimized at sub-therapeutic doses, whereas excessive disruption of tubulin organization at higher doses may saturate the apoptotic machinery or elicit counteractive cellular responses. This finding highlights a narrow therapeutic window for the combination, in which lower doses maximize synergistic effects and support clinical strategies to mitigate systemic drug toxicity.

In our study, the reduction in colony-forming ability and the suppression of motility further support the increased anti-proliferative and anti-migratory potential of the combination treatment. Migration is a critical

component of the metastatic cascade[21] and MT dynamics play a pivotal role in cytoskeletal rearrangements required for efficient motility[22]. Both agents exhibited significant inhibition of cell migration at combination doses of IC_{10} and IC_{30}, suggesting that dual targeting of MT turnover interferes not only with cell division but also with cytoskeletal reorganization, which is essential for cell movement. These findings are consistent with studies reporting that low-dose combinations of MT inhibitors can potentiate anti-migratory effects by altering MT organization[23-27].

Morphological assessments were performed using AO/EB staining to determine whether the combination treatment may induce features of apoptosis or necrosis. The observation of nuclear condensation and orange fluorescence in the combination settings indicates that enhanced cytotoxicity likely involves apoptotic mechanisms. In the context of MTAs, this morphological transition likely reflects a combined signaling event in which the simultaneous destabilization (by CHO) and stabilization (by PAC) of MTs generate a synergistic stress response. However, the molecular pathways underlying this effect remain to be clarified. Considering the roles of CHO and PAC in modulating Bcl-2 family proteins and caspase activation in various cancer models[28-30] including PC[19,31], future studies should investigate whether synergism observed in the study results from complementary modulation of MT-associated pathways or convergent activation of apoptotic signaling.

The findings suggest that the combined administration of CHO and PAC may hold potential as a therapeutic strategy for advanced PC.

Study Limitations

Although the present study provides valuable insights into the synergistic cytotoxic and anti-migratory effects of CHO and PAC on DU145 PC cells, certain limitations should be acknowledged. First, the results are based on a single PC cell line and, therefore, may not fully reflect the heterogeneity observed among different prostate tumor subtypes. Thus, the observed effects require further validation in additional PC cell lines, as well as in more physiologically relevant 3D tumor models. Second, apoptotic and necrotic effects were evaluated by AO/EB staining; however, the lack of flow cytometry-based quantitative apoptosis analysis is a limitation of the study. Finally, mechanistic analyses underlying the observed synergistic inhibition of the drugs were not included in this study. Future work should investigate the signaling pathways involved to validate the molecular mechanisms underlying these effects.

CONCLUSION

The present study demonstrates that CHO and PAC act synergistically at low doses to inhibit viability, proliferation, and motility in androgen-independent PC cells (DU145). These findings suggest that the combination of MTAs with opposing effects on MT polymerization dynamics may represent an effective strategy to enhance therapeutic efficacy while minimizing toxicity. Further investigation into the molecular mechanisms underlying the observed effect is necessary to elucidate the signaling pathways involved.

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Ethics

Ethics Committee Approval: This study does not involve human participants; therefore, ethical approval was not required.

Footnotes

Author Contributions

Concept: C.S., C.Sa., D.D.U., Design: C.S., C.Sa., D.D.U., Data Collection and/or Processing: C.S., C.Sa., M.A., D.D.U., Analysis or Interpretation: C.S., C.Sa., M.A., D.D.U., Literature Search: C.S., C.Sa., Writing: C.S., C.Sa.

Conflict of Interest: The authors declare that they have no conflict of interest related to this study.

Financial Disclosure: The authors declare they have no financial interests.

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