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Synergistic Effects of Cold Atmospheric Plasma and Chemotherapeutic Agents: Mechanisms and Therapeutic Outcomes

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ABSTRACT

Introduction: Chondrosarcoma (CS) is a rare malignant bone tumor characterized by marked resistance to chemotherapy and radiotherapy, leaving surgery as the primary treatment option. Increasing evidence suggests that cold physical plasma (CPP) exhibits antitumor properties through the generation of reactive oxygen and nitrogen species. Previous studies have demonstrated CPP-induced cytotoxicity in CS cells, which has led to increased interest in its potential synergy with routinely used chemotherapeutics. This systematic review evaluates current evidence on combining CPP with chemotherapeutics to enhance therapeutic responses in CS and related solid tumors.

Materials and Methods: A systematic search was conducted across PubMed, Scopus, and Web of Science for studies published between 2015 and 2025. Search terms included "Plasma Gases", "Drug Synergism", "Chemotherapy", and "Chondrosarcoma". Inclusion criteria comprised original research and review articles evaluated plasma-drug combination. Studies that did not evaluate plasma-drug combinational evaluation were excluded.

Results and Discussion: Studies included in this review consistently demonstrated that CPP combined with cisplatin, doxorubicin, or vincristine significantly enhanced cytotoxicity in CS cell lines compared to chemotherapy alone. Notably, the combination of CPP and doxorubicin yielded the most pronounced reduction in cell survival. Similar synergistic cytotoxic effects were reported in melanoma, breast, pancreatic, colorectal, glioblastoma, neuroblastoma, bladder cancer, and oral squamous cell carcinoma, with several *in vivo* models demonstrating tumor ablation following combined treatment.

Conclusion: Synergistic application of CPP with standard chemotherapeutics markedly enhances antitumor responses in CS cells and various solid tumors, primarily by strengthening apoptotic pathways and diminishing viability. Future studies should validate these synergistic effects in *in vivo* models of CS and optimize the dosing of plasma and drugs.



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Keywords: Chemotherapy, Chondrosarcoma, Drug synergism, Plasma gases

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