

DOSE-ENHANCEMENT EFFECT OF CYTOSTATIC AGENTS ASSOCIATED WITH INCREASED TEMPERATURE IN VITRO

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Background

The combination of chemotherapy and hyperthermia may be a promising approach in the treatment of malignant tumors. In the present study, the effect of 8 different chemotherapeutic agents in vitro was compared at 37°C and 42°C.

Materials and methods

Human cervical carcinoma HeLa cells, 24 hours after seeding, were treated with different concentrations of carboplatin, vinorelbine, ifosfamide, doxorubicin, etoposide, oxaliplatin, docetaxel or gemcitabine and incubated for 60 min at 37°C or 42°C. After the treatment the cells were left for 48 hours in the incubator at 37°C. The influence of chemotherapy and temperature on cell proliferation and survival was evaluated by hemocytometer cell counting using the Trypan blue exclusion method.

Concentrations of each drug causing growth inhibition by 50% and 90% (IC₅₀ and IC₉₀) and 50% initial population killing (LC₅₀) were determined. Thermal enhancement ratio (TER) for cell proliferation or cell death for each chemotherapeutic drug was calculated as IC₅₀, IC₉₀, or LC₅₀ for a drug alone divided by IC₅₀, IC₉₀, or LC₅₀ for the drug combined with hyperthermia.

Results

Reduced cell proliferation with increasing concentrations of chemotherapeutic agents was demonstrated. Hyperthermia alone caused only 10-20% growth inhibition. All the chemotherapeutic agents used demonstrated a dose-enhancement effect at elevated temperature. TER for cell proliferation for oxaliplatin, vinorelbine, carboplatin and ifosfamide exceeded 4, for doxorubicin and gemcitabine exceeded 2. TER for cell death did not exceed 1.3.

Conclusion

Synergism of hyperthermia and chemotherapy was clearly demonstrated for oxaliplatin, vinorelbine, carboplatin, ifosfamide and to a lesser extent for doxorubicin and gemcitabine. Thermal enhancement was most prominent with low drug doses.