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Short communication

Combination of chemotherapy, radiotherapy and hyperthermia *in vitro*

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Background: Combination treatments of radiotherapy with chemotherapy or mild-hyperthermia (temperatures in the range of 41–43 °C) are increasingly used for anti-cancer treatments. The combinations of two of these modalities have shown enhanced local control in the clinic [1]. There is a rationale for combining all three modalities [2], however there is limited pre-clinical and clinical data available to support this. In this study the effect of concentration, temperature and timing of tri-modality therapy, *i.e.* radiotherapy, chemotherapy and hyperthermia, on the survival fraction of cells is investigated.

Method: HT1080, human fibrosarcoma, cells were maintained in MEM medium, supplemented with 292 mg/L L-glutamine, 110 mg/L sodium pyruvate and 10% Fetal Bovine Serum. Cells were incubated for 1 h with doxorubicin (0, 0.02 or 0.06 μg/ml) in a water bath at 37, 42 or 43 °C before or after irradiation (0, 2, 4, 6, 8 and 10 Gy using a linear accelerator (Elekta, 6 MV)). Furthermore, cells were incubated for 1 h with doxorubicin (0.02 μg/ml at 37 °C), irradiated and subsequently incubated for 1 h in a water bath at 43 °C. In all cases, the individual modalities were separated by 45 min intervals. Finally, cell survival was measured using a clonogenic assay. Cell survival data was statistically tested in SPSS 23 (IBM, Armonk, NY, USA) by linear regression according to the LQ model [3].

Results: Only when doxorubicin was applied before radiotherapy an enhancement of the radiotherapy was present. Mild hyperthermia at 43 °C, but not at 42 °C, combined with radiotherapy resulted in an enhanced effect of the radiotherapy. In this case the largest enhancement was achieved when radiotherapy preceded hyperthermia at 43 °C. Finally, for three modality treatments, the combination of chemotherapy before and mild hyperthermia of 43 °C after radiotherapy resulted in the largest enhancement of radiotherapy, compared to any of the two modality combinations and to three modality treatments where chemotherapy and hyperthermia were applied concurrently.

Discussion and conclusion: The results that were obtained by combining two modalities (radiotherapy with doxorubicin or mild hyperthermia) were in line with previously reported data [4–6]. For all combination treatments the timing of the modalities is an important factor. The largest sensitization effect was achieved when doxorubicin is applied before and hyperthermia after radiotherapy. Most likely doxorubicin as well as hyperthermia interfere with the repair process of DNA breaks induced by radiotherapy [7,8] and thereby enhance the cytotoxicity of tri-modality treatment. Data published by Besse et al. in PlosOne [9]

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References

[1] Falk, IJH, (2001) .
[2] Jones, CCR, (2004) .
[3] Franken, Nature Protoc, (2006) .
[4] Li, EJ, (1977) .
[5] Watring, GO, (1974) .
[6] Hahn, CR, (1979) .
[7] Bonner, IJRB, (1990) .
[8] Kampinga, IJRB, (2001) .
[9] Besse, PlosOne, (2018) .

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