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Co-operative Radio-Immune-Stimulating Cancer Therapy

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ABSTRACT

Radiation therapy (RT) for cancer treatment is still delivered more or less in the same mode since Roentgen's discovery of the X-rays 1895. Conventional fractionated RT is given 5 days a week with a daily low dose of about 2 Gy until a high tumour target dose of about 60-70 Gy is achieved. This treatment regime which aims at eradicating the tumour by radiation induced cancer cell death has so far been one of the most successful modalities used to treat cancer. But despite substantial technical improvements in the current RT treatment modalities and despite the developments in chemotherapy (CT) the results of cancer treatment are not always successful. One reason might be that the traditional fractionated radiation therapy also decreases the number of tumour infiltrating T-cells (CD3+, CD4+, and CD8+) and thus prohibits immunogenic cell death.

During the millennium shift we found in a preclinical study that a single dose (6 Gy) of radiation dramatically enhances the effect of immune-therapy by using syngeneic tumour cell vaccine. This opens up for an interesting alternative to conventional fractionated RT regimes. This presentation summarizes the results of a number of pre-clinical studies from various researchers that demonstrate the enhanced therapeutic response of malignant tumours to various combinations of immunotherapy (IMU) with single fraction or hypo-fractionated radiation therapy (RT). The clinical trials of combining immune therapy and conventional radiation therapy which are carried out so far have, however, sparse effect. Clinical studies of combining established IMU regimes with a single 8 Gy fraction RT opens up the possibility for a closer co-operation between immunology and radiation. This therapeutic co-operative regime may also reduce the probability of relapse, and if relapse occurs the treatment can be repeated.

The strong infiltration of human tumours by activated CD8+T-Cells i.e. cytotoxic T lymphocytes (CTL) and CD4+ helper T(Th) cells is a hallmark for improved survival after therapy. But the presence of immune suppressive cells such as regulatory T-cells (T_{reg}), M2 macrophages and myeloid-derived suppressor cells (MDSC) in and around the tumour inhibit the action of CTL which counteract immunogenic tumour cell death. The Co-operative Radio-Immune-Stimulating Cancer Therapy involves the killing of the immune suppressing cells by a single high dose radiation (8 Gy) that opens a window for CTL to infiltrate the tumour and effectively induce immunogenic tumour cell death. The radiation effects also results in an increased release of tumour antigens and maturation of the dendritic-cells. This co-operative interaction of Radiation and Immune therapy is recognized as a breakthrough in cancer treatment that could result in successful treatment of radio-resistant tumours (pancreas, malignant melanoma, malignant glioma, lung etc) with a combination of Immune therapy. The low dose single radiation regime opens for possible treatment of colon and liver tumours as well.