Accelerated and hyperfractionated schedules

Analysis of the sets of data of accelerated, predominantly accelerated and hyperfractionated radiation treatments shows that, except with hyperfractionation and short single course accelerated regimens, the AD is not constant in consecutive weeks of treatment. High AD, above 25 Gy is typical for accelerated treatments when the dose is condensed into a single course in a short overall treatment time.

Conclusions

1. When fractionation regimens are altered to achieve a therapeutic gain through an increased tumour response relative to late normal tissue response, acute mucosal reactions become dose limiting in radiotherapy for head and cancer.
2. Acceptable risk of acute mucositis can be expected when the Dose-Time Ratio (DTR) is lower than 2.5 Gy x day -2 and accumulated dose per week (AD) is less than 12 Gy. Higher AC can only be considered if it is administered in no more than 2 consecutive weeks of 5-6 week treatment or 2-3 week split is given between series of high AD (or DTR).
3. High constant value of the AD (>14 Gy) during 5-6 weeks of treatment or the AD above 20 Gy and DTR above 10 Gy x day-2 lead to high risk of persistent confluent mucositis and consequential late necrosis which may occur within 4-8 months after treatment.

EFFECT OF IRRADIATION ON INTERLEUKIN 6 AND SOLUBLE INTERLEUKIN 6 RECEPTOR MODIFIED MELANOMA GENETIC VACCINE

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We have designed phase I/II human melanoma gene therapy clinical protocol. The aim of the study was to actively immunize HLA-A1 and/or HLA-A2-positive patients with melanoma with an admixture of irradiated autologous tumor cells and allogeneic melanoma cells genetically engineered to secrete IL-6 and sIL-6R in order to elicit or enhance specific and nonspecific anti-melanoma immune responses to autologous tumor cells to eradicate distant melanoma lesions. Irradiation of autologous and allogeneic tumor cells is a key step in preparation of cellular vaccine because of two major reasons, (i) it inhibits cell proliferation which is crucial in the case of autologous cells which may form a tumor; (ii) it increases melanoma vaccine immunogenicity. The aim of the study was to estimate the optimal dose of ionizing radiation which will provide sterilization of both autologous and allogeneic melanoma cells and will ensure cytokine secretion.

Human melanoma cells (Mich-1) were transduced with IL-6 and sIL-6R cDNA using double copy bicistronic retroviral vector. Parental and transduced cells were seeded at in six-well tissue culture plates and were irradiated with 10, 50, 100 and 200 Gy. Secretion of both recombinant proteins into culture was analyzed before and 24, 48, 72, 96 h and 6, 7, 10 and 12 days following irradiation. At the same time adherent cells were enumerated, evaluated for viability and proliferation. At 24, 48, 72 and 96 h postirradiation specific IL-6 and sIL-6R mRNA levels were analyzed.

Irradiation of gene modified cells inhibited their proliferation in the dose dependant manner. Dose of 50 Gy sufficiently affected cell proliferation, however, for safety reasons we decided to use the dose of 100 Gy for vaccine preparation. Irradiation did not inhibit secretion of IL-6 and sIL-6R. In contrary, on a per cell basis it significantly increased their secretion which lasted 12 days postirradiation. Interestingly, we did not observe dose or time dependent differences in specific mRNA cellular levels suggesting that increased secretion of both proteins is regulated not on the transcriptional but rather on the posttranscriptional level. Taking all these facts into account we concluded that irradiation of tumor cells may provide an effective and safe approach for gene-modified vaccine preparation.