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VOLUME EFFECT ON THE RADIATION INJURY OF RAT KIDNEY

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Purpose: To minimize the likelihood of radiation-induced kidney injury in treating tumors, the relationship of tolerance dose and irradiated volume of kidney should be known. We have used a rat model to determine the dose-response relationship when various volumes of the kidney are irradiated.

Methods and Materials: Anesthetized adult male rats (CD, 10-12 week old) were irradiated with 250 KV x-rays. The kidney was exteriorized and placed in a jig designed to shield all other tissues. Graded single doses were delivered to each of four volumes: 1/4V (half of one kidney), 1/2V (one whole kidney, or half of each kidney), 3/4V (one and a half kidneys) and 1V, where V is the volume of both kidneys. In addition, to compare radiation injury and surgery, partial nephrectomy was performed for 1/4V, 1/2V and 3/4V. Four to sixteen rats were used for each dose-volume point. The rats have been followed up for 540 days. The endpoints for the damage were: lethality, anemia, glomerular filtration rate, effective renal flow, and histology.

Results: We found that: (1) There was a threshold volume for radiation damage; injury did not occur if the volume irradiated was ≤ 1/2V, depending on the endpoints. (2) Median survival times did not depend on the dose when a small volume (i.e., 1/4V or 1/2V) was irradiated. (3) The LD_{50} (and the 95% confidence limits) at 450 days were 11.35 (8.08 to 12.13) Gy for 1V, 12.38 (11.08 to 13.40) Gy for 3/4V, 21.16 (17.21 to 26.56) Gy for 1/2V, and 28.80 (21.11 to 65.00) Gy for 1/4V. (4) The ED_{50} for animals with hematocrit level ≤0.36 at 365 days was 10.98 (4.96 to 13.67) Gy for 1.0V, and 13.82 (6.16 to 17.97) Gy for 3/4V. For 1/2V, only the 80% confidence limits could be derived, giving ED_{50}=40.14 (27.98 to ∞) Gy. (5) The results for all other endpoints were similar to those for hematocrit. (6) The dose response was the same whether to half of each kidney or one whole kidney was irradiated. (7) While the threshold volume for radiation injury was less than 1/2V, animals after 1/2V nephrectomy did not show a significant damage.

Conclusion: We conclude that a volume-dependent dose response exists, and the value of threshold volume depends on the endpoint used. The mechanism underlying the volume effect is complicated; the volume effect not only depends on the dose delivered to a specific volume but also depends on the response of both unirradiated and the survivors of the irradiated nephrons to the injury. Further, the existence of irradiated kidney affects the compensatory response of the intact nephrons.

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Radiosensitization in vitro by (E)-2'-(fluoromethylene)-deoxy-cytidine (FMdC), Pentoxifylline (PTX) or a combination.

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Purpose/objective:
To investigate the potential of FMdC as a ribonucleotide diphosphate reductase inhibitor, and PTX, as a methylxanthine derivative, to modify the radiation response of human colon cancer cell-line (WiDr) *in vitro*. The rationale of the combination is based on the known radiosensitizing effect of FMdC as a nucleoside analog. Flow cytometry done after irradiation shows an increase of number of cells in G2+M by pretreating these cells with FMdC. PTX is known to alleviate postirradiation G2+M block and subsequently radiosensitizes tumor cells. The objective of the study was to assess the possible interaction of FMdC and PTX.

Materials and methods:
The cell line was submitted for 48 hours in exponential growth conditions(at least two cell doublings), to a concentration of 30 nM FMdC. After subcultivation, cells were irradiated at low density at different doses (0-2-4-6 Gy) on an Oris-IBL cesium source (dose rate 80cGy/min). Immediately after irradiation PTX was added at a 0.25, 0.5 and 1 mM concentration. After incubation the cells were fixed and stained and colonies were counted. Survival fraction was calculated taking into account the intrinsic toxicity of FMdC, PTX and the combination. The ANOVA analysis was used which aims at testing the main effects of FMdC and PTX alone and their interaction. Flow cytometric analysis was done after labelling cells 48 hours after irradiation with propidium iodine in order to demonstate cell cycle effects.

Results:
FMdC (30 nM / 48 hours) prior to irradiation results in significant radiosensitization of WiDr; the SF-2 values decreases from 75.9 ± 3.9 to 62.3 ±1.8. For PTX alone added after irradiation, the SF-2 values expressed in % at 0.25, 0.5 and 1 mM are respectively 75.2 ± 1, 61.4 ± 1.6 and 55.1 ± 3.2. The combination of preirradiation FMdC (30nM) and postirradiation PTX (0.25, 0.5, 1mM) yields following SF-2 values: 55.6 ± 2.4, 45 ± 2.3 and 38.4 ± 3.8. The ANOVA analysis yields a significant reduction of SF-2 for FMdC (30 nM) and for PTX (0.5 and 1 mM) ($p < 0.001$); the p-value for PTX alone at 0.25 mM is 0.08. The interaction is additive. A separated analysis of the effect of PTX, allowing for the influence of FMdC, demonstrates the importance of the PTX-concentration (0.25 vs 0.5: $p<0.005$; 0.25 vs 1: $p<0.001$) and again FMdC is additive. Flow cytometric analysis shows a postirradiation accumulation of WiDr in G2+M, enhanced by preirradiation exposure to FMdC, but reduced if FMdC treated and irradiated cells are exposed to PTX.

Conclusions:
Both FMdC and PTX are radiosensitizers in vitro on WiDr. The combination of the effect of FMdC and PTX is additive. Cell cycle analysis indicates that the additive effect could be explained by alleviation of postradiation G2+M block.