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Treatment of 5-fluouracil induced diarrhea using octreotide acetate

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Object: Cytotoxic chemotherapy, particularly 5-Fluouroacil (5-FU), can cause severe diarrhea and octreotide acetate (OA) has a major therapeutic effect in the management of this complication. This prospective randomized study was conducted to investigate the efficacy of two different doses of OA in treating the severe diarrhea (NCI common toxicity criteria > grade 2) resistant to loperamide.

Method: We treated 36 pts with histologically documented colorectal or head and neck carcinomas. In 17 of these patients 100 igr of OA were administered subcutaneously thrice daily while the other 19 patients received 500 igr on a similar schedule.

Results: The OA was well tolerated by all patients and no side effects related to its use were recorded. Complete resolution of the diarrhea was achieved in 10/17 (58.8%) receiving 100 igr and in 18/19 (94.7%) of those receiving 500 igr ($p < 0.05$). The period required for complete remission of the diarrhea in the responsive patients was 2.27 days and 2.82 for the 100 igr and 500 igr respectively (NS).

Conclusions: This study has shown the significant benefit of using the escalated 500 igr dose of OA in treating 5-FU induced diarrhea. Although comparatively more costly this regimen becomes cost effective in view of the shorter hospitalization required for these patients.

Clinical radiobiology

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Effect of E2F-1 and E2F-1-mutants on the cellular survival and radiosensitivity

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Purpose: We are investigating molecular targets and methods to increase the radiation effect in radioresistant tumour cells.

Methods: The various phases of the cell cycle differ in their radiosensitivity and disturbance of cell cycle regulation can result in apoptosis. Overexpression of E2F-1wildtype (wt) and specific mutants (mt) thereof has been shown to deregulate S-phase of cells and induce apoptosis. We investigated the reproductive integrity, apoptosis and the radiosensitivity of isogenic mouse fibrosarcoma cells differing only in their p53-status after expression of E2F-1wt and a E2F-1mt lacking the cyclin A -binding domain.

Results: Increased expression of E2F1-wt reduced the survival rate of p53+/+ cells whereas the p53−/− cells were almost completely resistant to over-expression of E2F1-wt. Expression of the E2F-1mt overcame this resistance and induced apoptosis in both p53+/+ and p53−/− cells. The radiosensitivity of the p53−/− cells was much less compared to the p53+/+ cells. Overexpression of E2F1-wt increased the radiosensitivity of the p53−/−cells to a level comparable to the p53+/+ cells. The relative survival rate after 2 Gray (SF2) in p53+/+ cells was between 0.21 and 0.28 (with or without E2F-1wt/mt). The mean values of the SF2 in p53−/− cells were 0.7 without and 0.4 with E2F-wt.

Conclusion: Expression of E2F-1 derivatives results in a p53 independent reduction of the cellular survival rate and an increase of the radiosensitivity in radioresistant p53−/− fibrosarcoma cells to a level nearly comparable to radioresponsive p53+/+ cells.

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The role of FAS-FAS-ligand (FAS-L) interaction for radiation induced apoptosis in human lymphoma cells

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Introduction: FAS-FAS-L interactions induce apoptosis and are thereby a major regulatory tool within the T- and B-lymphocyte system. We provide evidence that an active upregulation of FAS-L is of major importance also for the induction of apoptosis in response to ionizing radiation.

Methods: Surface FAS-L expression on Jurkat cells was analyzed after 5 and 10Gy irradiation using FASC. Apoptosis was determined by Anexin V staining and subsequent FASC analysis and counting for apoptotic cells after acridine orange staining.

Results: Ionizing radiation induced an increased FAS-L expression 10–12 hours after irradiation. Preincubation of cells with an inhibitory antibody against FAS (ZB4) and FAS-L (NOK1) significantly inhibited the induction of apoptosis. Blocking the release of surface FAS-L into the media by matrix metalloproteinase inhibitors had no influence on apoptosis induction.

Conclusion: FAS-FAS-L interactions appear to play a major role for radiation induced apoptosis.

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Radiation-induces apoptosis in different pH environments in vitro

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Purpose: The effect of environmental pH on the radiation-induced apoptosis in tumor cells in vitro was investigated.

Methods: SCK mammary adenocarcinoma cells of A/J mice and human HL-60 promyelocytic leukemia cells were irradiated using a ^{137}CS irradiator and incubated in media of different pHs. After incubation at 37°C for 4–72 h the extent of apoptosis was determined using agarose gel electrophoresis, in situ TUNEL staining and flow cytometry.

Results: Irradiation with 2–12 Gy induced apoptosis in pH 7.5 medium within 4 h reaching a plateau level at about 48 h. The radiation-induced apoptosis progressively declined as the medium was lowered so that little apoptosis occurred in the first hours after irradiation with 12 Gy in pH 6.6 medium. However, when the cells were irradiated and incubated for 48 h in pH 6.6 medium and then medium was replaced with pH 7.7 medium, apoptosis promptly occurred.

Conclusion: An acidic environment markedly suppressed radiation-induced apoptosis, suggesting that the acidic intratumor environment may protect tumor cell from apoptotic death. The signals responsible for radiation induced apoptosis, however, appeared to persist in an acidic environment and triggered apoptosis when the acidity was eased. Changes in oxygen supply and blood flow during the course of fractionated radiotherapy may therefor affect the radiation induced apoptosis.

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Bax expression, apoptosis and proliferation prior and after preoperative radiochemo-therapy for locally advanced rectal cancer

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Purpose: To examine the association between apoptotic cell death, proliferative activity and the expression of the pro-apoptotic protein bax in rectal cancer before and after radiochemotherapy, this study was performed.

Methods: 32 patients, which were dispositioned to receive preoperative radiochemotherapy for locally advanced rectal carcinoma prior to radical surgical tumor resection were analysed. In all cases, pretherapeutical obtained biopsies and the final resection specimen after radiochemotherapy were available for analyses. The expression of the bax protein was assessed by immunoblotting and immunohisto-chemistry. Apoptotic cells were identified and quantified using the *in situ* end labeling (ISEL-) method. The