We have reported that intratumoral injection of boronated immunoliposomes can increase the retention of 10B atoms by tumor cells, causing tumor growth suppression in vivo with thermal neutron irradiation. In this study, we prepare a polyethylene-glycol (PEG) binding liposome (DPPC/cholesterol/DSPC-PEG2000) entrapped 10B compound for the application in clinical use of drug deliver sustem. We evaluated the cytotoxic effects of intrveneously injected 10B-PEG-liposome on human pancreatic carcinoma xenografts in nude mice with thermal neutron irradiation. After thermal neutron irradiation of mice injected with 10B-bare liposome or 10B-PEG-liposome, AsPC-1 tumor growth was suppressed relative to controls. Injection of 10B-PEG-liposome caused the greatest tumor suppression with thermal neutron irradiation in vivo. These results suggest that intraveneous injection of 10B-PEG-liposome can increase the retention of 10B atoms by tumor cells, causing tumor growth suppression in vivo upon thermal neutron irradiation.

718 PUBLICATION

Synergistic cytotoxicity by cis-platinum and neutron irradiation in human head and neck squamous cancer cells

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Purpose: Head and neck squamous cancer with poor response to cis-platinum chemotherapy also have poor response to subsequent radiation treatments. The purpose of this study is to investigate mechanisms underlying resistance to cis-platinum and photon irradiation in head and neck cancer cell lines and to study the effects of neutron irradiation on these resistant cell lines.

Methods: On five different head and neck squamous cancer cell lines, cytotoxicity of cis-platinum, photon irradiation, neutron irradiation, cis-platinum with photon irradiation, and cis-platinum with neutron irradiation was examined by clonogenic cell survival assay and sulforhodamine B staining. Neutron-mediated cell cycle regulation and apoptosis were also investigated by Annexin V staining and flow cytometric analysis.

Results: All five cell lines tested were more sensitive to neutron irradiation than photon irradiation. The relative biological effectiveness (RBE) of neutron relative to photon for 10%, 50%, or 90% tumor growth inhibition was 2.3–4.2. Neutron irradiation also enhanced cis-platinum cytotoxicity more efficiently than photon irradiation. G1 and/or G2/M cell cycle arrest was observed following photon and neutron irradiation, but more apoptotic cell death was seen with neutron irradiation than photon irradiation.

Conclusion: Synergistic cytotoxicity of neutron irradiation and cis-platinum suggests a potential clinical application in treatment for head and neck cancer, especially in patients with poor response to cis-platinum chemotherapy.

719 PUBLICATION

Rat model for radiation induced proctitis

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Purpose: During radiation treatment of pelvic malignancies, most patients experience side effects of proctitis. These side effects can cause treatment interruption that could result in decreased tumor control. This is the study to establish the optimal radiation dose in rat model for clinically compatible radiation-induced proctitis.

Materials and Methods: Female Wistar rats, weighing from 150 to 200 g, were employed. Using 6 MV LINAC, varying radiation doses (0 to 30 Gy) were delivered to the rectum of rat. On the 5th and 10th day after the irradiation, rectal specimens were grossly and microscopically evaluated. From this experiment, we selected 17.5 Gy for radiation-induced proctitis model. Rectal specimens were evaluated sequential gross and microscopic changes by time after irradiation (day 1 to day 14, and week 4, 6, 8, and 12).

Results: There was an increased mucosal damage with increasing radiation dose and a prominent mucosal reaction starting after 15 Gy irradiation. Rats treated with 17.5 Gy showed sequential post-irradiation changes ranging from mucosal edema and mild inflammation to ulcer and fibrosis. These findings were similar to changes found in radiation-induced proctitis of the human. No rats died due to bowel obstruction.

Conclusion: In summary, 17.5 Gy single fraction irradiation to the rat rectum is an ideal model for clinically relevant proctitis where we frequently experience bowel discomfort from swollen tissue but with rare incidence of side effects like mortality or obstruction. Also this study confirmed the dose related radiation injury of the rat rectum as other previous animal models.

720 PUBLICATION

Acute phase response during radiotherapy

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Introduction: The acute phase response is characterised by changes in the plasma concentrations of a number of liver synthesised proteins, one of which is C-reactive protein (CRP). Existence of these changes in the plasma profile underlies the change in erythrocyte sedimentation rate (ESR). Acute phase response itself is an illness and may be a result of immunological reactions and inflammatory processes. Plasma CRP level is frequently raised in inflammatory bowel disease, shock, trauma, surgery, infection, and myocardial ischemia. This study is designed to determine whether CRP level and ESR increase during radiotherapy (XRT) and whether these rises correlate with acute radiation morbidity.

Material and Method: Between April 1997 and October 1998, fifty-one patients with the diagnosis of endometrial or cervical cancer were treated with surgery and postoperative radiotherapy. Median age at the time of radiotherapy was 52 (26–73). Thirty patients received pelvic XRT, whereas 21 patients were treated by pelvic-paraaortic irradiation. A total dose of 50.4 Gy to the pelvis and 45 Gy to the paraaortic field with conventional fractionation was delivered. Erythrocyte sedimentation rates and CRP levels were studied at the beginning and at the end of XRT.

Results: The median ESR measurements before and after radiotherapy were 40 (8–100) and 43 (10–120) and median CRP levels were 0.59 (0.12–9.8) and 1.73 (0.12–32.2) respectively. The statistical analysis yielded significant rise in ESR and CRP levels at the end of the XRT ($p < 0.001$). The rise was more prominent in patients who were irradiated through pelvic-paraaortic field compared to the patients with pelvic radiation (p:0.005) and (p:0.028) respectively. There was no correlation between clinical severity of acute radiation enteritis and ESR and CRP rise in plasma.

Conclusion: Acute phase response is present during radiotherapy. Statistically significant increase in ESR and CRP levels in large irradiation volumes is observed, as expected due to more radiation- induced inflammation. Radiotherapy should be considered as a cause of increase in CRP level and ESR especially in clinical conditions where acute phase response is important.

721 PUBLICATION

Fundamental studies on the combination of intraoperative radiotherapy (IORT) and a hypoxic cell sensitizer PR-350 for pancreatic cancer

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Purpose: To investigate the radiosensitivity of human pancreatic cancer cells and the efficacy of PR-350 (doranidazole) which is being tested in phase I clinical trials in combination with IORT.

Methods: Four human pancreatic cancer cell lines (SUIT-2, PANC-1, BxPC-3 and MIA PaCa-2) and murine SCCVII cells were used. *In vitro,* radiosensitizing effects of PR-350 were investigated under aerobic and hypoxic conditions. *In vivo,* the tumor cells were implanted on the back of Balb/c nude mice, and the hypoxic fraction and the effects of PR-350 were assessed by an *in vivo-in vitro* assay.

Results: *In vitro,* PANC-1 and BxPC-3 were more radioresistant than SCCVII, while SUIT-2 and MIA PaCa-2 were similar in radiosensitivity to SCCVII. The sensitizer enhancement ratio (SER) was 1.25–1.3 at 0.4 mM and 1.4–1.55 at 1 mM in the 4 pancreatic cancer cell lines. These SER's were similar to those observed in SCCVII. The hypoxic fraction was 20% in SUIT-2 tumors and 27% in BxPC-3. The SER of PR-350 was 1.35 at the dose of 250 mg/kg. Investigation with the other tumors is in progress.

Conclusion: SUIT-2 and PANC-1 tumors had a reasonable proportion of hypoxic cells, which suggested the possible benefit of using a hypoxic cell sensitizer at IORT. PR-350 had definite radiosensitizing effect against these tumors.