516 POSTER

Combined effects of SU5416 and fractionated radiotherapy in tumor xenograft model

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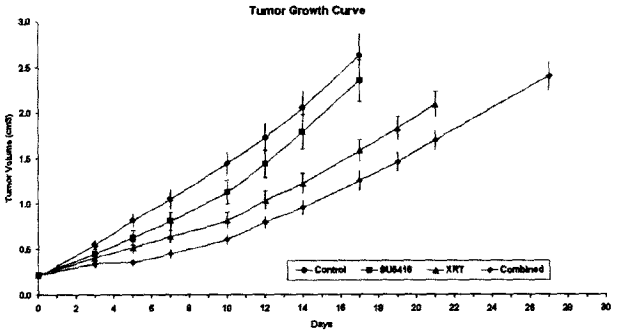
Background: Angiogenesis is critical for tumor development, growth and metastasis. Vascular endothelial growth factor (VEGF) is one of major regulators of angiogenesis. This study aimed to evaluate the combined effects of fractionated radiotherapy and SU5416 specifically inhibiting VEGF receptor 2 in tumor xenograft model.

Material and methods: NCI-H460 human lung cancer cells were inoculated into the thighs of 5-6 week old female athymic nude mice. Tumor volume was measured three times a week in 3 directions (width a, length b and thickness c) and calculated as 0.5abc. After tumors grew to a volume of 0.2 cm^3, treatment started with fractionated radiotherapy and/or SU5416. Radiation was delivered to tumor areas using a ^{60}Co irradiator with daily fraction of 2 Gy for 5 consecutive days (D0-4) and SU5416 of 25 mg/kg was administered i.p. every other day (D0/2/4). Treatment groups (20 mice each) consisted of control, SU5416 alone, radiation alone and SU5416 plus radiation. Tumor growth delay for a given treatment was calculated as the mean time it took for tumors to grow from 0.2 cm^3 to 2.0 cm^3 minus the mean time for control tumors. Dose enhancement ratio(DER) was also calculated using the equation; Tumor growth delay of combined treatment group minus that of SU5416 alone group divided by that of radiation alone group.



Results: There was no difference in weight change between 4 groups during the measurement period. Tumor growth delay for the treatment groups was 1.2 days in SU5416 alone group, 6.6 days in radiation alone group and 10 days in combined treatment group. DER was 1.33.

Conclusions: Combined use of SU5416 and fractionated radiotherapy showed moderate radiation enhancement effects in xenograft model using our drug dosage and administration schedule.

517 POSTER

Dose-dependent upregulation of YKL-40 by irradiation in human glioblastoma cells

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YKL-40 is a 40 kD extracellular matrix protein and a member of the mammalien chitinase-like proteins. YKL-40 stimulates proliferation of fibroblasts, endothelial cell migration and tube formation. YKL-40 has been proposed to be involved in tissue remodeling processes including cancer invasion and metastasis. Recently, YKL-40 has been found to be the most differential expressed gene in a microarray analysis of 19 glioblastoma multiforme (GMB) samples compared to normal brain tissue. A similar result was found in an oligoarray analysis of 4 GMBs versus normal brain tissue. Likewise, results in the SAGE database indicate high YKL-40 expression in GMBs compared to normal brain tissue. Serum levels of YKL-40 are elevated in high grade gliomas and have been suggested as a serum marker for malignant human gliomas, as well as a prognostic marker in several other cancers.

We have investigated 3 human glioblastoma lines for YKL40 expression. All three lines had YKL-40 mRNA expression but only U87 secreted YKL-40 protein in measurable amounts. U87 was investigated for YKL-40 expression after ionizing radiation. Cells were exposed to 0, 2, 5, 10, and 20 Gy of ionizing radiation and conditioned media was harvested after 24 and 48 hrs. The YKL-40 level in the media was determined by ELISA. A dose-dependent increase in YKL-40 production up to more than 3-fold was found 48 hrs after radiation. This was confirmed on the mRNA level by Northern blot. mRNA was harvested 18, 24 and 48 hrs after radiation and interestingly, the rise in YKL-40 mRNA was not observed until 48 hrs after radiation. Again we found a dose dependent response.

The late but pronounced rise in YKL-40 levels after irradiation indicates that YKL-40 production is a downstream response mediated by other proteins rather than an immediate response to radiation. The increase in YKL-40 levels after irradiation suggests the involvement of YKL40 in a cellular stress response, which is in agreement with earlier reports of YKL-40 expression during inflammation and tissue remodeling - two processes involved in the progression of malignancy.

518 POSTER

Carbon ion beam treatment at the Hyogo Ion Beam Medical Center (HIBMC)

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Background To confirm the acute toxicity and response for patents with so called radio-resistant tumor treated by carbon ion beams in the HIBMC as well as stability of the treatment machine.

Material and methods Thirty patients with malignant tumor originated in head & neck (19 patients), lung (3), liver (6), or bone & soft tissue (2) were enrolled in a clinical trial based on the Good Clinical Practices regulated by the Minister for Health, Labour and Welfare in Japan. Patients were required to have an ECOG performance status of grade 2 or less, localized tumor within 12 cm in diameter and WBC >= 3,000/mm3. The relative biological effectiveness of carbon beams was 1.23 to 2.56 by preclinical investigations. There were 17 males and 13 females. All patients had radio-resistant tumor consisting of malignant melanoma in 8, hepatocellular carcinoma 6, adenocarcinoma 5, adenoid cystic carcinoma 4, esthesioneuroblastoma 2, undefferentiated carcinoma 1, mucoepidermoid carcinoma 1, clear cell carcinoma 1, liposarcoma 1 and chordoma 1. Treatment planning was performed using a 3-D radiation treatment planning system. When treating patients with lung or liver cancer, respiratory gating system was used. Just after irradiation, treatment volume was confirmed by auto-activation positron emission tomography. Prescribed dose was 57.6 gray equivalent (GyE) to the 4MVX rays /16Fr/4wks in H & N cancer, 68.4GyE/9Fr/3wks in lung cancer, 52.8GyE/8Fr/2wks in liver cancer, and 70.4GyE/32Fr/8wks in soft tissue and bone tumor. The acute toxicity was assessed according to the criteria of the NCI-CTC up to 90 days after starting carbon irradiation. Objective tumor response was evaluated at the four to six weeks after completion of the treatment using both the WHO criteria and FDG-PET images.

Results Full courses of carbon therapy consisted of 443 portals in the 30 patients were given exactly as scheduled without any trouble of the accelerator or treatment system. Average beam time per fraction was 97 sec. No patients experienced severe acute local reactions more than grade 3. Two patients were CR, 16 PR, and 12 NC. The response rate (CR+PR) was calculated 60%. Of 26 patients who were evaluable in FDG-PET, 21 (80.8%) decreased in standardized uptake value of the tumor after treatment.

Conclusions Our treatment units and systems are safe and reliable enough for carbon irradiation to be used for several malignant radio-resistant tumors localized in the body.

519 POSTER

Technical factors associated with radiation pneumonitis after adjuvant breast irradiation

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Background: To assess the incidence of, and clinical factors associated with clinically significant symptomatic radiation pneumonitis(RP), which requires steroid medication after tangential breast/chest wall irradiation with or without regional lymph node radiotherapy.