1218

HOW SHOULD NICOTINAMIDE BE USED CLINICALLY TO OVERCOME HYPOXIC CELL RADIORESISTANCE IN HUMAN TUMOURS?

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Nicotinamide, either alone or in combination with carbogen breathing, is currently undergoing preliminary clinical testing as a means of overcoming radioresistance in tumours that results from the presence of hypoxic cells. However, how nicotinamide should be given has not been entirely established. Our studies, in which plasma samples were taken from human volunteers after oral ingestion of nicotinamide and analysed by HPLC, showed that the peak plasma concentration (± 1SE) after taking 6 g was 159 μg/ml (± 15). Identical peak plasma levels were found in mice after an intraperitoneal injection of 171 mg/kg (± 16). Such concentrations in mice will produce maximal enhancements of radiation damage, provided the radiation is given at the time of the peak concentration, which in our human studies was within 1 hour after ingestion. Additional experimental studies by us have also shown that nicotinamide primarily eliminates perfusion limited acute hypoxia in tumours, thus its clinical potential should be when combined with any treatment that can attack diffusion limited chronic hypoxia. Carbogen breathing is only one of many possible strategies that can be used in this context and whether or not this is the best agent to combine with nicotinamide is currently under investigation and the results will be presented.

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1219

FLOW_CYTOMETRIC DNA ANALYSIS AND BrdUrd LABELLING INDEX IN BRAIN TUMOURS

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The proliferative potential and DNA ploidy of 35 highly malignant and 24 low-grade gliomas were investigated using bromodeoxyuridine (BrdUrd) incorporation and flow cytometry. Tumour samples (1-3) from each patient were incubated in vitro for one hour in 37°C with BrdUrd using a high preasure oxygen method. Both the percentage of BrdUrd-labelled cells (labelling index, LI) and total DNA content were evaluated. Seventy four per cent of high-grade and 51 per cent of low-grade tumours were judged aneuploid. The tumours showed variability in the LI values which ranged from 0.21 to 13.3 per cent. The mean LI value was 3.42 and 1.98 per cent for highly malignant and low-grade tumours, respectivelly.The mean intratumoral variability amounted to 32 per cent and was much lower than intertumoral. The correlation between the LI and further course of disease should assess the cell kinetic study as a possible prognostic factor in radiotherapy of CNS tumours.

1220

THE EXTENDED LINEAR-QUADRATIC MODEL --- THE POLYNOMIAL APPROXIMATION OF THE CELL SURVIVAL CURVES

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GG Steel(1989): The Linear-Quadratic equation is simply regarded as an empirical relationship that successfully fits a wide range of actual cell survival data, and according to Taylor's formula, any mathematical fuction can be approximate by polynomial. Therefore, $SF=e^{-(\alpha D+\beta D^2+\gamma D^3+\cdots+---)}$ or $-\ln SF=\alpha D+\beta D^2+\gamma D^3+\cdots+---$ should be theoretically a better approximation than L-Q model. There is no difficulty in the estimation of the isoeffects, using this extended model: $(\alpha+\beta d_1+\gamma d_1^2+\cdots+---)D_1=(\alpha+\beta d_2+\gamma d_2^2+\cdots+---)D_2$ There is also an easy way to expressed isoeffect dose, if applying NTD_2(Noramlized Total Dose based on 2Gy per fraction, Yang and Flickinger, 1990) concept. The 1st derivative of -lnSF means the direction of the survival curve and the 2nd derivative of -lnSF means the concavity point of the inflection of the survival curve.The explanation of the cell killing of the extended model is similar to L-Q model, that is, the α killing, the irrepairable and the non-α killing, the repairable.

1221

TUMOR CONTROL PROBABILITY FOR HUMAN SOFT TISSUE SARCOMA XENOGRAFTS IN MICE.

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The TCD_{50} assays were performed to assess local radiocurability of human soft tissue sarcoma xenografts in nude and SCID mice. Three cell lines were studied. Intramuscularly growing tumors were irradiated with single doses at five days after inoculation (micro), or at a diameter of 6.5 mm and 8.5 mm, under aerobic and hypoxic conditions in parallel assays. In SCID mice, for cell line coded STS26T, TCD_{50} values in "micro" size assays were 22 Gy and 47 Gy for aerobic and hypoxic conditions, respectively. TCD_{50}s for 6.5 mm xenografts were 49 Gy and 59 Gy, in air and in hypoxia, and for 8.5 mm of 48 Gy and 56 Gy, respectively. Similar values were obtained for the other two cell lines. TCD_{50} values were not different between SCID and nude in relation to the same tumor size and conditions of irradiation. A significant difference in TCD_{50} values between "micro" and 6.5 mm sizes but not between 6.5 mm and 8.5 mm was found. TCD_{50} in hypoxia condition for "micro" size was 2.14 times that of aerobic condition. However, for the 6.5 mm and 8.5 mm xenografts it was 1.2 and 1.17, respectively.

Our data on three sarcoma xenografts indicate that the higher probability of control is best achieved in microscopic tumors and under aerobic conditions.

1222

THE PATTERN OF NK CELL ACTIVITY IN CANCER PATIENTS FOLLOWING IN VITRO IRRADIATION

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Sixteen cancer patients suffering from different malignancies were studied for the pattern of NK cell activity following in vitro irradiation before, during and after external radiotherapy. The cells were irradiated by an 8 MV linear accelerator at nine different doses in the range between 100 and 1200 cGy. NK activity in vitro increased, but not significantly, in patients in an early stage of disease between fractions of 200 and 600 cGy. No change was observed in patients with advanced disease. Previously, we have shown a significant increase in NK activity in the peripheral blood of healthy controls irradiated in vitro with fractions between 100 and 600 cGy. NK activity in normal subjects was significantly modified by in vitro irradiation. No such effect has been observed in cancer patients.

1223

3D CONFORMAL RADIOTHERAPY BY DYNAMIC PROTON BEAM SCANNING ON A COMPACT ISOCENTRIC GANTRY: THE PILOT FACILITY AT PSI IS NEAR COMPLETION.

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The new proton therapy facility, presently under construction at PSI, is planned to start its medical program in late 1994. The application of the dose to the patient will be performed by rapid scanning of the focused proton beam in 3 dimensions under complete computer control (spot scanning method - superposition of individually controlled Bragg peak spots - at a rate of about 5000 spots/minute), using multiple fields on a compact proton gantry (4 m diameter). This method gives maximal flexibility and provides automated 3d dose conformation on a routine basis. Due to the favorable physical characteristics of protons, the dose distributions for deep seated tumors treated with protons with this new technique are expected to be clearly superior to those obtained with photons, even when compared to the most advanced techniques. The medical program aims at the introduction of new indications for proton therapy, including especially large and/or irregularly shaped tumors. The project should show the feasibility of this efficient modern approach to proton therapy as a first step toward the introduction of protons in the hospital.