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PILOT STUDY OF NIMORAZOLE WITH "CHART" IN ADVANCED HEAD AND NECK CANCER

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Preliminary results of CHART suggest a modest improvement in local control of T3-4 head and neck cancer with a suggestion of lower morbidity compared with conventionally fractionated radiotherapy. Hypoxia may be an important cause of failure of CHART, because of the reduced time for reoxygenation. Hence we investigated the possibility of using the hypoxic cell sensitizer nimorazole with CHART.

Patients with stage IV head and neck cancer were entered into a pilot study. All were treated to a dose of 54 Gy in 36 fractions in 12 consecutive days, with three fractions of 1.5Gy 5½ hours apart. Three groups were studied: one received 1.2g/m^2 nimorazole before the first fraction each day: the second received an additional 0.6g/m^2 before the midday fraction: the third received 0.6g/m^2 before the midday and evening fractions. Estimates of plasma levels of the drug showed that on average each dose gave a plasma level ≥ 30μg/ml at the time of irradiation. Drug toxicity was mild and there was no evidence of accumulation of the drug in the plasma during the 12-day course. Acute radiation toxicity was not enhanced in comparison with our previous experience of CHART, and early tumour responses appeared promising.

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SUPPLEMENTARY TREATMENT WITH ISOTRETINOIN COMBINED WITH INTERFERON-A-2A IN THE PRIMARY RADIOTHERAPY OF INOPERABLE CERVICAL CANCER - RESULTS OF A CLINICAL PHASE-II-STUDY.

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Background: irresectable cervical cancer is normally treated by combined radiotherapy with external irradiation and high-dose-rate-brachytherapy. Several previous in-vivo- and in-vitro-studies suggest an improvement of radiosensitivity in squamous cell cervical cancer by the addition of retinoids (cRA) and interferon-α-2a (IFNα-2a) to radiotherapy.

Materials and methods : in a pilot study, 22 women with cervical cancer (stage IIb-IIIb) were recruited. All received 6 Mio.I.U. IFNα -2a sc./daily and 1 mg/kg Isotretinoin p.o./d for 12 days prior to radiotherapy. During radiotherapy the dosages were decreased to 3 Mio I.U. three times weekly and Isotretinoin 0.5 mg daily. The patients were treated with external radiotherapy (15-MV photons) and Ir-192-high-dose-rate-afterloading to a total dose of 70 Gy in point A and 54 Gy in point B.

Results : all patients tolerated the treatment well, the toxicity was mild. Grade III/IV-complications did not occur. 13 patients with completed treatment were evaluable for response, 9 patients are under therapy. CR was achieved in 11 patients (85%), PR in the remaining 2 patients. The long-term effect cannot be stated yet.

Conclusions: pretreatment with IFNα-2a/cRA is well tolerated and yields high complete remission rates. Further evaluation seems useful.

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DOES APPLICATION REGIME INFLUENCE THE EFFICACY OF G-CSF TREATMENT IN RADIATION INDUCED LEUKOPENIA?

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Background : Iatrogenic leukopenia can cause delay or discontinuation of radiation treatment. This complication can be overcome with the use of granulocyte colony-stimulating factor (G-CSF). However, no reliable data exist regarding the mode of G-CSF application. Therefore, the efficacy of two administration strategies of G-CSF in irradiated patients was compared in a prospective randomised clinical study.

Material and methods : Forty-one patients who developed leukopenia whilst undergoing radiotherapy were treated with G-CSF at a daily dose of 5 μg per kg. The first group received single injections of G-CSF when required (n = 21). The second group received G-CSF on at least 3 consecutive days (n = 20). An analysis of leucocyte counts, the number of days on which radiotherapy had to be interrupted and the side effects of growth-factor treatment was performed.

Results: an incrase in leucocyte values in the peripheral blood was observed in all patients treated with G-CSF. In the group which received G-CSF when required, 2 injections (range: 1-8) were administered in most cases. In the second group, most of the patients received 3 injections (range : 3-9). The average duration of therapy interruptions was 4.8 days (0-28) in the first therapy arm and 2.5 (0-20) in the second arm. The variance in the duration of therapy interruptions between the 2 groups was not significant (p = 0.2).

Conclusions : our results reveal that G-CSF is effective in the treatment of radiation induced leukopenia regardless of the mode of application. The administration regime can be adapted to the clinical situation in question.

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USING A MULTILAYERED CULTURE OF SiHa CELLS TO STUDY THE PENETRATION OF ANTICANCER AGENTS

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A new method of cell culture has been developed which permits the growth of multilayered cell cultures. These cultures have several features in common with solid tumours growing *in vivo* and can be used to study the effects of anticancer agents. Depending on growth conditions these cultures have reached thicknesses of up to 50 cell diameters and exhibit varying and predictable proportions of hypoxic cells. Diffusion dependent (chronic) hypoxia develops in cultures greater than 20μm in thickness and perfusion dependent (acute) hypoxia can be modelled by intermittently interrupting the oxygen supply.

Using multilayered cell cultures composed of SiHa cells, we have investigated the penetration of the bioreductive cytotoxin tirapazamine and the hypoxic cell radiosensitizers misonidazole and etanidazole. In the hypoxic cell radiosensitizer studies, individual multilayered cell cultures were irradiated at different times after being incubated with misonidazole or etanidazole. The time taken for the radiosensitizers to penetrate to the hypoxic cells residing in the central layers of the multilayered cell culture was probed by assessing cell survival. In the studies of bioreductive cytotoxins, pre-irradiated multilayered cell cultures were exposed to tirapazamine for different periods and the penetration monitored using fluorescence microscopy and cell survival.

The results of these studies indicate the ability of bioreductive cytotoxins and hypoxic cell radiosensitizers to penetrate tumour tissue and suggest that multilayered cell cultures can be useful in studying the activity of anti-cancer agents.