Miscellaneous

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TAXOL AS RADIOSENSITIZER IN VITRO: IS THE G2/M BLOCK A PREREQUISITE?

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Taxol, a novel diterpene compound, has a unique mechanism of action by promoting the microtubule (MT) assembly and preventing their depolymerization, thus accumulating the cells in the most radiosensitive phase of the cell cycle, G2/M.
On this rationale we examined the combined action of Taxol-radiation exposure on two radioresistant tumour cell lines: A549 (lung adenocarcinoma) and A375 (melanoma).
At subcytotoxic doses of taxol ranging from 1 to 3 nM we observed an increase in cell kill by low doses of radiation. The sensitising enhancement ratios (SER) obtained at 3nM concentration of taxol were 1.8 for A549 and 3.0 for A375. The pattern of Taxol cytotoxicity is modified by radiation exposure so as the concentrations needed to kill cell are lower than those which block cells in mitosis. However at these radiosensitising concentrations we failed to demonstrate, on flow cytometry a G2/M block. It seems therefore that accumulation of cells in radiosensitive phases of cell cycle may not be the only mechanism of in vitro radiosensitisation by this drug.

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GLUTATHION (GSH) FOR PROTECTION OF CISPLATINUM (CDDP) INDUCED NEURO- AND NEPHROTOXICITY

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CDDP is a widely used antitumor agent effective in the treatment of solid tumors. Efforts to improve the response rates in advanced disease by escalating the dose have been limited by unacceptable toxicity. Based on experimental and clinical studies indicating that reduced GSH is a protective agent against CDDP-induced neuro- ,oto-, and nephrotoxicity, a randomized clinical trial with high dose CDDP including GSH (Group A) or intensive hydration (Group B) was designed for patients with advanced Non small cell lung cancer (NSCLC) or Squamous-cell-carcinomas of the head- and neck (SCC). To date, a total of 21 patients (pts)(18 males,3 females) with a median age of 54 years (range 35-74) entered this study (NSCLC:n=5;SCC: n=16; all stage III and IV). All pts received 80 mg/m^2 CDDP + VP-16 or 5-FU every 4 weeks for a minimum of 3 cycles.Pts in group A (n=11) received 5 g of GSH before CDDP therapy and 2000ml of normal saline. The control group B (n=10) received 4000ml of normal saline and forced diuresis only. A median of 5 cycles (range 1-10) has been given to these pts (median observation time: 17 months, range 5-29). 15/21 pts were currently evaluable for response (4pts early deaths, 2 withdrawals). The overall response rate was 14/15 (93%) pts (CR: 2/14=14%, PR 6/14=43%, SD 6/14=43%). The response rate in group A was 8/9 (89%) pts (CR 2/8=25%, PR 2/8=25%, SD 4/8=50%). In group B the overall response rate was 6/6 (100%) pts (CR 0/6; PR 4/6=67%, SD 2/6=33%). 16 pts were evaluable for myelotoxicity, nephrotoxicity and neurotoxicity: We observed in 3/9 (33%) pts of group A and in 5/7 (70%) pts of group B severe neutropenia (WHO grade IV only in group B). Nephrotoxicity was noticed in 1/16 (6%) pts (group B). Ototoxicity and neurotoxicity, evaluable in 10/20 pts, were mild and comperable between the two groups. This preliminary data shows, that GSH might be a protectic agent against CDDP-induced toxicities, with allows the reduction of hydration therapy and forced diuresis, without reducing anti-tumor activity of the cytotoxic agent.

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PHASE II TRIAL OF INTERFERON-γ (IFN-γ) / INTERLEUKIN-2 (IL-2) FOR ADVANCED RENAL CELL CARCINOMA (RCC)

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Numerous clinical studies showed efficacy of biological response modifiers (BRM) in the treatment of advanced RCC. In this phase II study, we investigated efficacy, toxicity, and feasibility of IFN-γ in combination with IL-2 in patients with advanced RCC. One cycle of therapy consisted of 100 mcg IFN-γ sc 3x/week for two weeks, 4.5 MIU IL-2 sc over four consecutive days for the next two weeks followed by a two week rest period. 3x500 mg/day paracetamol are given orally for the first two weeks of therapy to prevent or mitigate flu-like symptoms. To date 40 patients (25 males/15 females) with a median age of 59 years (range: 44-81 years) have been accrued to the study. A median of 3 therapy cycles (range 1-9) have been given to these 40 patients (median time of observation: 5 months, range: 1-18 months) and all patients are eligible for feasibility and toxicity evaluation, and 31 patients for response documentation, respectively. 32 of the patients were trained in self-application of the cytokines and 8 patients preferred the application of therapy through their family doctor. No WHO-grade III or IV toxicity has been documented so far. Side effects consisted of flu-like syndrome grade I/II in 21 patients despite prophylactic paracetamol, local erythemas after IL-2 application in 18 patients, and hypotension grade I mainly after IL-2 application in 4 patients. Myelotoxicity was mild in general and consisted of grade I/II leucopenia and thrombocytopenia only. No red cell transfusions had to be given. Response data of 32 patients after a median time of observation of 10 months (range: 5-16 months) are as follows: CR: n=2 (6%), PR: n=3 (9%), SD: n=14 (44%), PD: n=13 (41%). Our preliminary data show that a treatment with IFN-γ/IL-2 is not only associated with low toxicity, but also very practical for out-patients, and offers therefore a good quality of life. The antitumor activity of this therapy in patients with advanced RCC is proven by the response rate (CR+PR+SD) of 59 %.

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ORTHOTOPIC LIVER TRANSPLANTATION (LTX) +/- NEOADJUVANT CHEMO-THERAPY IN UNRESECTABLE HEPATOCELLULAR HEPATOMA (HCC) - A PROSPECTIVE RANDOMIZED TRIAL

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HCC is the most common malignant tumor of the liver. Live expectancy after diagnosis is < 6 months and > 90% of the patients die from their disease. For patients with unresectable HCC only LTX offers a chance for survival. However, the rate of long term survivors is small since the majority of the patients relapse after LTX and die within two years. Thus, LTX for HCC is discussed controversially. But since no other treatment is currently available, LTX remains the sole therapeutic option with a chance for cure. Cytostatic chemotherapy is of little value in the treatment of wide spread disease. Only with doxorubicin, the most active single substance, objective responses can be achieved in 20-30% of the patients with no impact on survival. Based on the result of a phase II study with neoadjuvant doxorubicin, in which a >50% 3-year survival rate was reported, we designed a prospective randomized trial comparing LTX with LTX and neo-adjuvant doxorubicin in order to evaluate the impact of neoadjuvant therapy upon disease free and overall survival. Chemotherapy consists of 20 doses of doxorubicin 15 mg/m² given pre-, inter-, and postoperative in weekly to two-weekly intervals. The number of the pre- and postoperative treatment cycles is variable depending on the availability of the donor organs. So far 11 patients have entered the study and 4 patients in the neoadjuvant treatment arm have underwent LTX. No major treatment related toxicity or complications were observed. The preliminary feasibility and toxicity data will be presented.