New Drug Development

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CHEMOTHERAPY INDUCED EMESIS. MANAGEMENT OF EARLY AND DELAYED EMESIS IN MILDER EMETOGENIC REGIMENS

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The objective of the study was to examine the problem of control of nausea and vomiting induced by non-cisplatin cyclophosphamide-based chemotherapic regimens in breast cancer patients.
This was a randomized, double-blind, parallel-group and placebo controlled study comparing the efficacy of four antiemetic therapeutic regimens (A:Ondansetron for 3 days; B:Ondasetron plus Metoclopramide; C:Granisetron given a single dosis and D:Ondansetron given in a single dosis) in breast cancer patients receiving Cyclophosphamide, Methotrexate and 5-Fluoracil (CMF) regimen (174 cycles) and Cyclophosphamide, 4-Epiadryamicin and 5-Fluoracil (FEC) regimen (132 cycles). Both, number of emetic episodies (early and delayed emesis) and quality of life were evaluated.
In patients receiving CMF there were no differences between regimens A, B and C in controlling early emesis. The single dose Ondansetron regimen (D) showed the worst resuts (**p=0.003**). Delayed emesis was best controlled by the "3 days-regimens" (A and B). In patients administered a FEC treatment, the antiemetic efficacy was superior for the single Granisetron regimen (C) if early emesis was considered. Moreover, efficacy of single Granisetron dosis (C) was similar to the 3-days Ondansetron regimen (A) in controlling delayed emesis after FEC treatment. The single Ondansetron regimen showed again the worst results (**p=0.007**).
Despite different antiemetic schedules, nausea and emesis are significant problems in patients receiving cyclophosphamide-based chemotherapy.

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ROLE OF ANTIESTROGENS AS ANTIFIBROTIC AGENTS.

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A young patient with Gardner's Syndrome and a huge multi recurring retroperitoneal desmoid tumor has been recently trated with the anti estrogenic Toremifene (T) drug and a colliquative necrosis of the tumor has been obtained. The antiproliferative effect of T in desmoid tumors remains unknown. At high doses T appears to exert a cytolitic effect indipendent of its antiestrogenic action. T may stimulate stromal fibroblast to produce TGF beta a negative paracrine growth factor for epithelial cells. TGF beta is the cytokine that initiates and terminates tissue repair, and whose sustained production underlies the development of tissue fibrosis. In rats with pulmonary fibrosis experimentally induced total lung TGF content was several times higher than in normal rats. In humans with idiopathic pulmonary fibrosis Tgf beta 1 is increased in alveolar walls. The increased production of TGF beta preceded the synthesis of collagen, fibronectin and proteoglycans. The Authors intend to evaluete experimentally the T efficacy of influencing on the synthesis of TGF beta and of preventing pulmonary fibrosis. Toremifene could have a role as usefull antifibrotic agent.

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CHARACTERIZATION OF A PROTEIN WHICH RECOGNIZES DNA DAMAGED BY MINOR GROOVE BINDERS.

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Some DNA minor groove binders have shown antiviral and antitumor activity. The distamycin derivative Tallimustine and the CC-1065 derivative Adozelesin and Carzelesin are under clinical investigationin phase II clinical trials. The mechanisms of repair of the DNA lesions caused by these drugs are unknown. By using the gel retardation assay, we have identified a protein able to recognize a fragment of DNA only if it was previously reacted with minor groove binders (MGB). This protein binds with very high affinity AT containing DNA treated with MGB such as Distamycin A or Hoechst 33258 but not with a major groove binders (such as e.g. quinacrine mustard). This protein was found to be present in extracts of human, murine or hamster cells, although the human protein appears to have a molecular weight slightly lower than that of the other species. This protein is expressed both in cancer and normal tissues. By using ultrafiltration techniques as well as Southwestern analysis it was estimated that the apparent molecular weight is close to 100 Kda. Work is in progress to purify this protein which might be involved in the recognition and repair of DNA damage caused by minor groove binders.

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THE SIDE EFFECTS OF PACLITAXEL IN SOLID TUMORS

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The paclitaxel is a relativelly new cytotoxic agent, used in the treatment of the breast and ovaria cancer. However, its efficacy is also studied in other histologic types of tumors. We have administered a total number of 69 cycles of this drug in our department. We have observed the main side effects of paclitaxel, which has been used either as monotherapy or in combination with other cytotoxic drugs.
Alopecie has developed in all of the patients, in 2 patients an early allergic reaction developed, we could report leukopenia of Grade 3 in 3 patients. Peripheral neurotoxicity was detectable in 5 patients, but in all of these cases the cis-platinum has been also used.