New Drug Development

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EFFICACY OF MITOXANTRON IN TREATMENT OF TUMOR'S PLEURISY AND ASCITES.

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Aim of study: determining of the intracavitary instillation of Mitoxantron ("Germed" Germany) for treatment of cancer's pleurisys & ascites. The optimal dose -30mg for one instillation in one cavity was chosen with 5 weeks interval. 37 patients have been treated, CS=IY, f/m = 33/4: 20 patients had pleurisys, 13-ascites, 4-polyserositis.
Efficacy criteria: CR - absence of fluid in the treated cavity during > one month. PR - fluid appeared in the treated cavity during first month of follow up but the quantity was small & evacuation was not needed. Most effective Mitoxantron was in patients with pleurisy (overall efficacy 70%, CR-20%, PR-50%). High efficacy was determined in patients with ascites (92%), but CR was only in one case. Most effective treatment was in breast and ovarian cancer patients. Other cases with stomach cancer, lung cancer & mesotelioma appeared non sensitive.

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CLONES OF A HUMAN OVARIAN CANCER CELL LINES EXPRESSING WILD-TYPE OR MUTATED p53 AS A MODEL FOR STUDYING NEW ANTICANCER AGENTS. M. Broggini, F. Vikhanskaya, A.M. Codegoni, P. De Feudis and M. D'Incalci. Istituto "Mario Negri", Milan, Italy.
The tumor suppressor gene p53 has been reported to play an important role in the repair of DNA damage induced by different agents. To better study new compounds which can interact with this protein, we transfected a human ovarian cancer cell line which does not express p53 neither at RNA nor at protein level with p53. We utilized a plasmid coding a temperature sensitive mutant which expresses mutant p53 at 37°C and a wild-type like p53 at 32°C. Among the different clones obtained we selected a clone (SK23) which, at 37°C maintains growth characteristics similar to the parent cell line. Upon shifting to the temperature of 32°C this clone reversibly changes its morphology and stops growing because of the presence of the wild-type p53. Since p53 has been found mutated in most of the human cancer, this system can represent a useful model for studying new compounds directed against this target. This system will be discussed initially in relation to response to classical DNA damaging agents such as melphalan, cisplatin and doxorubicin.

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MECHANISM OF ACTION OF A BENZOYLNITROGEN MUSTARD DERIVATIVE OF DISTAMYCIN (FCE24517).
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FCE24517 is a novel antitumor agent synthetised by Farmitalia Carlo Erba laboratories which is undergoing early clinical trials. It binds to the minor groove of DNA and alkylates N3adenine in a highly sequence-specific manner. To investigate its mode of action we used tumor cell lines well characterised for their N-methylpurine-DNA glycosylase, O6-alkylguanine-DNA alkyltransferase activity or for deficient excision repair mechanisms. In addition FCE24517 activity was investigated in cells transfected with the bacterial tag gene encoding for N3-methyl adenine-DNA glycosylase; in cells not expressing p53, expressing the mutated p53 or a wild type like p53; in Saccharomyces cerevisiae and isogenic rad 9 deletion mutant. The studies indicate that the mode of action of this drug is different from that of conventional alkylating agents and highlight the relevance of cell cycle arrest and DNA repair mechanisms. More in general the study shows the potential of the use of genetically and biochemically defined cell systems to identify and investigate the mode of action of novel and potentially more selective anticancer agents.

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ANTI-ESTROGENIC THERAPY IN METASTATIC COLO-RECTAL CANCER
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Since estrogen receptors were found in gastro-intestinal cancers, anti-estrogenic therapy was considered as a new alternative in treating patients suffering from this disease.
Clinical trials with the anti-estrogen tamoxifen showed tumor remissions only singular in patients with advanced colorectal cancer. Thus, it was concluded that potentially no receptor mediation is installed but other mechanisms are responsible fo the steroid hormone effects in so-called non-target tissues. To reveal this non-rececptor mediation our study was to find out whether anti-estrogenic therapy is successful in hormone-receptor negative colorectal cancer or not.
A newly developed anti-estrogen, Droloxifene, was given orally to ten patients suffering from metastatic colorectal cancer after completing palliative surgery. Seven patients showed tumor progression, only one patient seemed to stay in stable condition.two patients were excluded from or left the study on their own shortly after initiation of treatment due to a prefinal status without being observed long enough to get usable results.
Anti-estrogenic therapy seems to be ineffective in hormone-negative colorectal carcinomas. A proof for non-receptor mediation could not be seen.