Symposium no. 7

Tumour Drug Delivery

7.001

PERIPHERAL HEMATO-IMMUNOLOGICAL MODIFICATIONS INDUCED BY SUBCUTANEOUS (SC) rIL-2 TREATMENT OF ADVANCED NEOPLASMS.

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Seven pts with advanced cancer were treated with SC rIL-2 (Proleukin-Cetus) with 9 million IU/mqx2/die for 2 days followed by 1.8 million IU/mqx2/die for 5 days/ week for 6 cycles and peripheral hemato-immunological modifications were evaluated and compared to base values:

	2°-3° cycles	6° cycles
Eosinophils	10 times +	6 times +
Monocytes	3 times +	2 times +
Total Lymphocytes	4 times +	2 times +
IL-2R and CD69	5 times +	2 times +
sIL-2R	5 times +	3 times +
CD4-CD8	4 times +	base values
CD16	2 times +	1 time +
sCD4-sCD8	1 time +	1 time -

At present, we are evaluating if these modifications correspond to clinical response.Partially supported by AIRC

7.002

OINTMENTS WITH METHOTREXAT FOR ONCOLOGICAL USE

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We realized a series of new ointments with Metrotexat (MTX) destined for treatment of dermic and breast exulceratives cancers . The ointments associated actively and potentiated reciprocally the citostatic effect of MTX ,with the reepithelizant , antibacterian , soothing , nutritive effect of bee wax , with the rehydrative effect of methyl cellulose (MC), pectine (P) with or without mineral salts (MS) (Na ,K , Ca , Mg chlorides) . The composition of the ointments is : bee wax 15 g. , Cholesterol 1 g., sol. NaHCO3 ,2 % 10 g., MTX 20 mg.,Dist.Water 15 g. , MC.0,1 % 15 g.,P 0,4 % 15 g., Ol.parafini ad 100g. By use of ointments for treatment of 12 breast exulceratives cancers were obtained good results in 11 cases after 6 weeks of 4 - 6 daily applications. Our results recommended the use of oint - ments with MTX as adjuvant in treatment of breast exulceratives cancers .

7.003

CISPLATIN (CDDP) AND MITOXANTRONE (DHAD)AS A FIRST LINE CHEMOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER.

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CDDP represents one of the most active drugs in non-small cell lung cancer(NSCLC).Moreover,recent data would suggest that DHAD may synergize with CDDP in the treatment of NSCLC.Based on these data,a study was started to evaluate the efficacy of a chemotherapeutic regimen containing CDDP and DHAD as a first line chemotherapy in advanced NSCLC (CDDP:60 mg/m2,DHAD 12 mg/m2 i.v. day 1 every 21 days for at least 2 cycles).The study included 16 patients(pts),14 of whom were fully evaluable (epidermoid carcinoma:6;adenocarcinoma:7;large cell carcinoma:1). A partial response(PR)was achieved in 5/14(36%) pts,without any significant relation to histotype; 2 pts (14%)had a stable disease,while the last 7 cases(50%)rapidly progressed.Toxicity was mild in all cases. We suggest that CDDP plus DHAD is an effective and well tolerated chemotherapeutic regimen in the therapy of NSCLC, even though its activity does not seem to be higher than that obtained with more conventional chemotherapies.

7.004

A PERTUSSIS TOXIN-SENSITIVE G-PROTEIN IS INVOLVED IN ADRIAMYCIN-INDUCED HISTAMINE RELEASE AND UPTAKE IN RAT PERITONEAL MAST CELLS.

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Adriamycin induces a non-cytotoxic histamine release from rat peritoneal mast cells with biochemical characteristics similar to that of basic secretagogues, that is connected with a very high affinity of the antineoplastic drug for mast cells and has been correlated with its cardiotoxicity. The mechanism through which non-immunological secretagogues induce exocytosis is not yet clarified but it has been suggested that activation of a pertussis toxin-sensitive GTP-binding protein is involved. The aim of this study is to check if adriamycin-induced histamine release and uptake are sustained by a similar mechanism.

Pertussis toxin (100 ng/ml), which interferes, via ADP ribosylation with some G-proteins, inhibits histamine release and adriamycin uptake in rat peritoneal mast cells. Pretreatment of mast cells with neuraminidase (0.1 U/ml), which hydrolyzes sialic acid residues, decreases the secretagogic effect of the adriamycin and its uptake. These results suggest that sialic acid residues might be involved in the initial binding of the antineoplastic agent which activates a pertussis toxin-sensitive G-protein and then induces exocytosis and adriamycin uptake.

7.005

LEVAMISOLE AND 5-FLUOROURACIL AS ADJUVANT TO SURGERY IN PREVENTION OF LIVER METASTASES OF A TRANSPLANTED RAT COLONIC ADENOCARCINOMA

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The effect of surgery plus adjuvant therapy with levamisole and 5-FU on the development of liver metastases of a large bowel tumor in the rat model was studied. The tumor was a transplantable spontaneous adenocarcinoma which was generated by injecting 1 x 10^5 tumor cells into colon wall. Twenty one days thereafter the tumor was surgically removed and animals were allocated to the following regimes: no treatment, levamisole, 5-FU, and the combination of levamisole and 5-FU. The presence of liver metastases and immunological status of the animals was exzamined. Significantly fewer adjuvant-treated animals developed liver metastases than those undergoing surgery alone ($P < 0.05$-0.001). In conclusion, adjuvant therapy with levamisole plus 5-FU did suppress the growth of metastases of adenocarcinoma in the liver and gave a survival advantage.

7.006

Cytotoxicity, incorporation and metabolism of N-L-Leucyl-doxorubicin in doxorubicin-sensitive and resistant human breast cancer cells in culture.

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N-L-leucyldoxorubicin (leudox) is a new derivative of doxorubicin (dox) which is presently in clinical phase I study. We have evaluated its cytotoxicity, incorporation and metabolism in doxorubicin-sensitive and -resistant human breast cancer cells in culture (MCF-7). We have observed that the IC50 of leudox was about 2-3 times higher than that of dox both in sensitive and resistant cells. Leudox and dox incorporation in the cells was followed up to 24h of incubation ; this incorporation was very rapid both in sensitive and resistant cells and a plateau was reached within 30mn of incubation, whereas dox incorporation was slower. Dox itself underwent no metabolism in the cells, but leudox was progressively metabolized into dox, so that concentrations of leudox and its metabolite were equivalent after 24 hours of incubation. These results suggest that leudox behaves as a prodrug of dox, giving rise to the active species within the tumoral cells.