NCy 27

First treatment results with carboplatin and iproplatin in various tumors.

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Carboplatin (JM8) and Iproplatin (JM9) are new platin analogues, which are actually being evaluated for antitumor effectivity. Their main advantage is that they are expected to be less nephrotoxic than the original compound cis-platinum.
As participants of a multicenter trial, we have treated 26 patients up to now. 20 of them are evaluable, and out of these, 8 patients had bronchogenic carcinoma, 5 patients had soft tissue sarcoma, 3 had malignant mesothelioma of the pleura, 2 patients had head and neck tumors, 1 had colon cancer and another cancer of the renal pelvis.
13/20 patients had received prior chemotherapy, 7/20 had prior radiotherapy. Age range was 24 to 70 years (median: 50 years). Patients were randomised for treatment.
Treatment consisted of JM8 400 mg/m² (heavily pretreated patients 360 mg/m²) or JM9 300 mg/m² (pretreated patients 270 mg/m²) as an 30 minutes infusion, repeated every 4 weeks. No hydration therapy was used.
Up to now, we have seen 1 Partial Remission (PR) in a patient with soft tissue sarcoma, and 2 PR in patients with head and neck tumors.
Side effects were nausea and vomiting in 13 out of 20 patients, this was more pronounced with JM9 treatment as compared to JM8. Leucopenia was seen in 6/20 patients, thrombopenia in 4/20 patients. No renal toxicity was seen. The study is being continued.

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NCy 28

ANTITUMOR ACTIVITY OF A DIPLATINUM COMPLEX OF THE NAPHTHAZARINATO BINUCLEATING LIGAND

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The tetracycline part of the anthracycline antibiotics can be considered as a derivative of the anthraquinone molecule.Some of the substituted anthraquinones,especially some substituted naphthazarins such as alkannin and shikonin have antitumor activity(Paull et al.J.Med.Chem.19,337, 1975,Sankawa et al.Chem.Pharm.Bull.25,2392,1977). As a result of trying experiences to make complexes containing both the cisplatin and adriamycin moieties,we thought to be advisable to synthesize coordination compounds containing naphthazarine instead of tetracycline.
The structure of the main compound we tested is confirmed by analytical methods and by IR and NMR spectra.It is a crystalline black solid with the stoichiometry $Pt_2(C_{10}H_4O_4)(NH_3)_4Cl_2$,stable in air,soluble in DMF and DMSO but insoluble in water and most of the common organic solvents.It is planar with 2 inequivalent Pt-O bonds.The naphthazarinato ligand brings two platinum centers in an end-to-end fashion.
The diplatinum complex was tested against leukemia L1210.Ehrlich ascites tumor,adenocarcinoma AC-755,leukemia P388 and melanoma B16.Comparative work has been done with cisplatin and the ligand.The LD_{50}(15 days) is 60mg/kg ip.The complex has against all the above tumors activity comparable with that of cisplatin.The nephrotoxicity of the complex is much more lower than that of cisplatin.Also gastrointestinal toxicity is lower.

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NCy 29

PHASE-I-CLINICAL-STUDY OF 24 HOUR INTRAVENOUS INFUSION OF DOXIFLURIDINE FOR 3 MONTHS

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The aim of this open, non-comparative, 2 centre clinical-pharmacokinetic trial was to determine the maximum acceptable monthly dose and patient acceptability of 5dFUR by continous daily i.v.infusion. 17 patients with advanced or metastatic solid tumours who may or may not have received prior chemotherapy or surgery entered the 3 month trial. The first patient (table 1) was treated according to an ascending dose schedule starting with 0.5g/m². As long as no cardiotoxic or neurotoxic symptoms or other adverse effects of WHO grade 2 severity developed, the daily dose was increased at weekly intervals by increments of 0.5g/m².

Table 1: Weekly Doxifluridine Dose and Adverse Effects of Pt.No. 1

Week No.	1	2	3	4	5	6	7	8	9
Dose(g/m²)	0.5	1.0	1.5	2.0	2.0	Pause	1.5	1.0	1.5
Adverse Effects					L(3)		N(2) S(2)	N(1) S(2)	N(2) S(3) HFS(3)

L=leucopenia;S=stomatitis;N=nausea;HFS=hand-and-foot-syndrome; ( )=WHO grade of toxicity

Following development of severe HFS in Pt.No. 1, a protocol amendment was made so that the next 9 patients were treated with a fixed dose of 1.0g/m².In 6 patients HFS developed.

A further 7 patients entered the protocol on a fixed daily dose of 0.75g/m². In 3 of these patients we found only a mild form of HFS.
No neurotoxicity of cardiotoxicity has been observed. Except for Pt.No.1, leucopenia was at most Grade 3.
The results indicate that a daily dose of 1.0g/m² 5d'FUR by 24 hour i.v.infusion is unacceptable due to development of HFS. In ongoing Phase-II-trials, patients will be treated with a daily dose of 0.75g/m².

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NCy 30

FIRST RESULTS OF A CLINICAL TRIAL WITH PROTEIN A-IMMUNADSORPTION IN PATIENTS WITH EITHER MESTASTATIC COLON CANCER OR c-HUS.

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Protein A (SPA) is a cell wall component of pathogenic Staphylococci.It binds nonspecifically to the Fc portion of the IgG molecule and has a preferential binding of IgG-immune complexes (IC).- Preliminary investigations indicated that circulating IC (cIC) could act as "blocking factors" in patients with early stages of colon cancer disease. In patients with adenocarcinoma who develop a cancer associated hemolytic uremic syndrom.(c-HUS) IC may play a role in the so far unknown etiology. The c-HUS consists of thrombocytopenia, microangiopathic hemolytic anemia and progressive renal failure, with a mortality rate of 80% within 12 months from estblishment of the diagnosis. In general, this entity develops in patients whose tumors are either in a complete or partial remission after mitomycin-C chemotherapy. High levels of cIC with substantial platelet aggregatory activity are normally present in the sera.-A clinical study was started to prove the therapeutical benefits of SPA-immunadsorption in both groups of patients and to investigate the possible mechanisms of immunmodulation after protein A treatment. So far 4 patients with c-HUS and 2 patients with colon cancer entered the study. The two colon cancer patients had advanced local recurrence of the disease and in one case there were additional pulmonary metastases. Both patients did not respond to a chemotherapy trial with sequential MTX/5-FU. - The treatment procedure consists of bi-weekly SPA- immunadsorptions of 30%-40% of the plasma volume, followed by the same chemotherapy regimen the patients got before recurrence. Adsorption capacity for IgG of the 200 ml-columns used was 25 mg/ml gel. Both patients had positive IC levels which dropped to normal levels after the treatment. There was an impressive hemorrhagic necrosis of tumor mass leading to partial response. The treatment is continued at the present time.- Patients with c-HUS represented with decreased complement levels, suggesting an ongoing inflammatory process. In 4/4 patients a dramatic hematologic improvement occurred, with fall in serum LDH, rise in haptoglobin, platelets,followed by rise of hematocrit and complement levels. The circulating IC disappeared. There was a stabilisation of renal impairment.- The median symptom free survival time is now 17,3 months. On average, response was achieved after 5 treatments over a period of 10-14 days.

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