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PHASE II TRIAL OF 5-FLUOROURACIL(F), ETOPOSIDE (E) AND CISPLATIN (P) IN 5 DAYS (FEP-5) FOR ADVANCED GASTRIC CANCER (GC).*Constela M, Barón FJ, Rubiales AS, Barrajón E, Calvo L, Otero J, Mel JR, Cueva J and Lacave AJ*, Grupo Oncológico del Noroeste. Dept.Medical Oncology. Hospital General de Asturias*. 33006 Oviedo. Spain.*

From May 1991 until May 1992, 34 patients(pts) were treated with P 20 mg/sq m iv in 1/2 hr. days (d) 1-5 with a prehydration of 1/2 hr., E 40 mg/sq m in an infusion of 1 hr. after P d 1-5, and F 1 gr/sq m over 22 hrs. d 1-5 every 4 weeds. Two pts were ineligible (Karnofsky<60% and renal function <60%) and 2 pts were not evaluable for response (lost for evaluation and no evidence of evaluable disease). In the 32 eligible pts it was possible to evaluate toxicity and survival. The characteristics analysed were: sex, age, histology, extent of the disease, Karnofsky and type of surgery.There were 4 C.R. and 9 P.R. with an averall response rate of 43.3%, N.C.(at least for 3 months) in 30% and P.D. in 26.6% of the pts. M duration of response was 8 mon. (6-16+) and M survival time 9.5 mon. (0.3-16+). The maximum toxicity in each patient was recorded according to the WHO. The nadir of the hemoglobine, leucocytes and thrombocytes was 9.8 (7.2-12.3), 2,500 (200-11,700) and 112,000 (37,000-826,000) respectively. Nine pts experimented aplasia and 6 of them sepsis. Two of these pts died (one of them had a long-standing and apparantly inactive ankylosing spondylitis). The percentage of non-hematologic toxicity grades 3 and 4 were: alopecia 43%, stomatitis 28%, vomiting 25%, diarrea 12%, dizziness 3%, tiredness 3% and neuropathy 3%.In conclusion, FEP-5 is an active regimen in GC, however it has an importan toxicity. Since the number of CR seems to be superior to our previous experiences with FP further studies with less toxic schedules are warranted.

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ADJUVANT COMBINATION CHEMOTHERAPY (AMF) POSTPONES RECURRENCE IN A RADICAL RESECTED CARCINOMA OF THE PANCREAS AND PAPILLA OF VATER

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After radical resection 61 patients with carcinoma of the pancreas (n=47) or papilla of Vater (n=14) were randomised between chemotherapy and control. The drug regimen AMF: doxorubicin (40 mg/m²), mitomycin C (6 mg/m²) and fluorouracil (500 mg/m²), were given once every third week for six cycles (n=30), whereas the control group had no adjuvant chemotherapy (n=31). The 1, 2, 3 and 5-year survival in the AMF group were 70, 43, 27 and 4% versus 45, 32, 30 and 8 in the control group. Median survival time in AMF group was 23 months compared with 11 in the control group (p=0.02, median test). Two patients with cardiotoxicity and nephropathy were recorded in the AMF group. One patient died of septicemia.

CONCLUSION: The AMF regimen delayed the occurrence of recurrence, but had no effect of long-term survival.

Drug Development

Clinical Pharmacology

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TAXOL® METABOLISM IN HUMAN PLASMA

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Taxol is a representative of a relatively new group of antineoplastic agents which act as microtubuli assembly promoters. Taxol has proven activity in several phase I and II studies against breast and platinum refractory ovarian cancer.

Liver metabolism and/or extensive plasma binding and tissue distribution may play an important role in plasma disappearance. Only 5-10% unchanged Taxol is excreted by the kidneys. Several metabolites have been detected in rat and human bile. Until now no metabolites have been observed in human plasma. By using a highly sensitive HPLC technique with solid phase extraction we are able to quantitate Taxol and metabolite concentrations (as taxol equivalents) as low as 10 ng/ml in plasma.

In a group of 30 patients with ovarian carcinoma, 11 possible metabolites were observed on chromatographic analysis. 3 Metabolites were found by UV-photodiode array detection to have a taxane structure. The amounts of the other 8 metabolites were too minute to allow further analysis. Further structural identification studies are ongoing. The retention times of Taxol with this assay is about 10 minutes. The retention times for the three major metabolites using this assay are 4, 5 and 7 minutes. This indicates that these taxanes are more polar than Taxol. Baccatin III, a natural precursor of Taxol with no cytotoxic activity, was not detected.

These results indicate that Taxol is metabolised, and putative metabolic products can be found in plasma of patients treated with the drug.

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ETOPOSIDE PHOSPHATE (EP): A COMPARATIVE INTRA-PATIENT BIO-EQUIVALENCE STUDY WITH ETOPOSIDE(E)

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EP is a water soluble analogue of E. In our phase I study (Proc AACR: 3165; 1992) leucopenia was dose limiting and a daily dose of 100mg/m² for 5 days q3 weekly was recommended for further study. At this dose 24 patients were randomised to receive EP or E with subsequent cross over. Plasma pharmacokinetic sampling for E and EP was performed on day 1 and day 5 using reverse phase HPLC with UV detection following solvent extraction and ion pair reverse phase HPLC with fluorescence detection following solid phase extraction, respectively. EP is only detectable during and immediately after infusion. Bioequivalence as measured by E AUC was 80 - 120%. Haematologic toxicity is equal after equivalent doses of E and EP. EP is an effective water soluble pro-drug for E that gives equivalent pharmacokinetic and haematologic toxicity *in vivo* to that of the parent compound.