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TAXOTERE IS ACTIVE IN ADVANCED GASTRIC CARCINOMA: RESULTS OF A PHASE II CLINICAL TRIAL

A Sulkes, F Cavalli, A van Oosterom, S Kaye, J Wanders, H Franklin, for the EORTC Early Clinical Trials Group/NDDO (Amsterdam) and N LeBail, M Bayssas, Rhone-Poulenc, France.

Twenty-six evaluable patients (pts) (17 males, 9 females), median age 59 yrs (range 44-72) and median PS 1 (0-2), with advanced, untreated, measurable gastric Ca were given taxotere, 100mg/m2 IV over 30' without premedication, Q3W. Metastatic sites included the liver in 7 pts and retroperitoneal lymph nodes in 8; 6pts (23%) achieved a partial remission, for a median of 3+ms (2-6+). An additional 6 pts (23%) showed stabilization of disease.Pts have received a median of 2 cycles of taxotere (1-8) for a total of 53 cycles. Hematological toxicity consisted mainly of non-cumulative granulocytopenia, median nadir (day 7) 0.36/mm^3 (0.06-3.15), with 5 episodes of leukopenia and fever; non-hematological toxicity included universal alopecia, mild N&V, and allergic reactions with skin rash and pruritis. Two pts had supra-ventricular arrhythmia. Dose reduction was necessary in 18 cycles; there have been no drug-related deaths. Our preliminary data indicate activity of taxotere in gastric Ca. Updated results will be presented.

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COMBINATION 5-FLUOROURACIL (FU), FOLINIC ACID (FA) AND ALPHA-INTERFERON 2B (IFN) IN ADVANCED GASTRIC CANCER

E. Jäger-Arand*, H. Bernhard**, O.Klein, B. Wächter*, F. Theiss*, B. Baumann-Baretti*, W. Dippold**, K.-H. Meyer zum Büschenfelde** and A. Knuth*
* Onkologische Klinik, Krankenhaus Nordwest, Frankurt, Germany,
** I.Medizinische Klinik, Johannes Gutenberg-Universität, Mainz, Germany

Based on encouraging treatment results with FU/FA or FU/IFN in gastrointestinal tract cancer, a pilot study was initiated to evaluate the effects and toxicity of combinaion FU/FA/IFN in patients (pts) with inoperable/metastatic gastric cancer. **Schedule**: IFN 6 M. U. s.c. 1x/week, FU 500mg/qm bolus i.v. 1x/week in the middle of a 2-hour infusion of FA 500mg/qm 1x/week. Of 57 entered pts, 50 (18 females, 32 males) are evaluable for response and toxicity (3 early deaths, 4 too early). Median age was 54 years (33-73), median Karnofsky performance status was 85% (60-100). Sites of measurable tumor manifestation were: inoperable primary tumor/local recurrence (11), liver metastasis (8), lymph nodes (18) and peritoneum (12). **Toxicity**: 1/50 pts had WHO grade 4 toxicity (diarrhea), 4/50 pts had WHO grade 3 toxicity (nausea 1, diarrhea 3). Except for 1 treatment limiting grade 4 toxicity, no modifications of dose or schedule due to toxicity were requiered. 36/39 pts experienced significant reduction of tumor related pain under treatment. **Results**: 7/50 pts experienced complete response, 11/50 pts partial response, 13/50 pts minor response, 17/50 pts tumor stabilization and 2/50 pts progressive disease. Median duration of response was 5.5+ month, median progression-free intervals 4.5 months, median survival time has not been reached yet. **Conclusion**: Biochemical modulation of FU with FA and IFN is effective in locally advanced and metastatic gastric cancer. Moderate toxicity, treatment in an outpatient setting and high response rates of tumor related pain contribute to an effective palliation.

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PHASE II STUDY OF GEMCITABINE IN PATIENTS WITH ADVANCED PANCREATIC CANCER. J. Carmichael[1], U. Fink[2], R. C. G. Russell[4], M. F. Spittle[4], A. Harris[3], G. Spiessi[2], J. Blatter[5].
[1] Nottingham General Hospital, Nottingham, UK; [2] Technical University, Munich, Germay, [3] ICRF Clinical Oncology Unit, Churchill Hospital, Oxford, UK; [4] Middlesex Hospital, London, UK; [5] Lilly Germany, Bad Homburg, Germany.

In a US phase II study gemcitabine has shown activity in advanced adenocarcinoma of the exocrine pancreas (5PR/39pts). We report the results of the 3-centre european study using a schedule of Wx 3 Q4 with a 30 minute infusion and a starting dose of 800 - 1000 mg/m². No patient had previous chemotherapy. 33 patients were enrolled with 28 evaluable for efficacy having received at least 2 courses of gemcitabine. Reasons for non evaluability: 4 early progression, 1 early death due to progression. Characteristics of the 28 patients: 18 male, 10 female, median age 55, WHO performance status 0 = 10, 1 = 16, 2 = 2. Twenty five patients had metastatic disease. A total of 82.3 courses and 247 injections were given.

Gemcitabine has been well tolerated. Overall, toxicity was mild. WHO Grade III myelosuppression was associated with only 3 infusions. The most common reason for dose omission/reduction was leukopenia (23 infusions) and thrombocytopenia (10 infusions). Twenty one doses were given at an escalated level (1200 mg/m²) following completion of 1 cycle at standard dose with minimal toxicity.No WHO Grade IV changes in haematological or biochemical parameters occurred, except in progressing patients (1 thrombocytopenia in a patient with pre-existing anemia and 1 AST and 1 alkaline phosphatase Grade IV). Symptomatic toxicity was mild with no toxicity greater than WHO Grade II, except that Grade III Nausea/Vomiting which occurred in 14 cycles. The most common symptomatic toxicities were WHO Grade I and II fever in 11/82 courses and rash in 8/82. There was no alopecia, pulmonary or cardiac toxicity, nor any significant change in renal function.

Two patients have had independently validated partial responses (7% PR, 95% CI 1-24%), 1 in liver, the other in the primary tumour. These were accompanied by pain relief and reduced analgesic requirement. Nine patients had stable disease, 17 patients progressed. Median duration of progression free time is 11.5+ weeks (range 3 - 26 weeks). 20 patients were evaluable for assessment of the disease markers, CEA Ca 19-9 and Ca 195. Of these 8 patients showed decreases in markers, with stabilisation in further 4 patients. Major reductions in markers were seen in the two patients who had partial responses and in 2 patients out of 5 with minor responses. In phase II trials gemcitabine has shown activity which compares favourably with that achieved with fluorouracil-based combination regimens (± leucovorin; ± IFN a 2 B). Further evaluation including the examination of the effect of schedule and infusion-time is warranted.

Keywords: Gemcitabine, pancreascancer, solid tumors

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PHASE II TRIAL OF TOPOTECAN IN ADVANCED PANCREATIC CANCER

R Scher, CJ Lusch, F Green, R Kosierowski, M Simmonds, PF Engstrom, PJ O'Dwyer
Fox Chase Cancer Center and the Fox Chase Network, Philadelphia, PA 19111 USA.

Topotecan is a semisynthetic water-soluble derivative of camptothecin with pronounced antitumor activity in preclinical models. Topotecan exerts its cytotoxic effects through inhibition of topoisomerase I, high levels of which in tumor cells correlate with sensitivity to the drug. In an ongoing Phase II trial, we have treated 15 patients with advanced or metastatic pancreatic cancer with topotecan 1.5 mg/m^2 as a 30-minute infusion daily for five days; courses were repeated every three weeks. The median age was 60 years (range 31-85), median performance status 1, and no patient had prior chemotherapy. The major toxicity was leukopenia, which was grade 3 in seven and grade 4 in two patients. Thrombocytopenia was grade 3 in one, grade 4 in two patients. Other side-effects included diarrhea (grade 3) in two patients and elevated LFTs in one. Among 15 evaluable patients antitumor activity was observed in three; one patient had a partial response lasting two months and two had a minor response. This study demonstrates preliminary evidence of the activity of topotecan in pancreatic cancer.

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LIVER TRANSPLANTATION (OLT) FOR SMALL HEPATOCELLULAR CARCINOMA(HCC) IN CIRRHOSIS

V.Mazzaferro,E.Regalia,G.Colella,L.Gennari

Liver Unit - Istituto Nazionale Tumori
V.Venezian,1 20133 Milan ITALY

From January 1991 to February 1993 27 OLT were performed in 25 patients affected by HCC in cirrhosis. The acceptance criteria chosen for the prospective accrual of such patients were: 1) non resectable single nodule < 5 cm or multifocal HCC (< 3 nodules,< 3 cm) 2) pre-operative T1-2,N0,M0 3) histologically proven cirrhosis. Pre-operative Child-Pugh stage was A=7 pts, B=8 pts, C=10 pts. In 17 pts (68%) pre-OLT chemoembolization (CE) with Lipiodol, Gelfoam and Doxorubicin, Mitoxantrone or Mitomycin C was feasible. Although a necrosis of > 50% was observed in 40% of the HCC-nodules,the exact role of CE on pts-survival is still not clear since no tumor recurrence is detected yet. Perioperative mortality (1st month) was 16%, one (4%) non oncological late death (9months) occurred. Post-transplant HCC stage was pTx=2, pT1-T2=14, pT3=7, pT4=2. Lymphnodes were free of tumor in all cases. One-year survival of the series is 80% and up to now all deaths are due either to post-OLT complications (ARDS,GVHD,multiple organ failure and sepsis) or to HBV recurrence. No tumor recurrence has been observed after a median follow-up of 12 months.
OLT for HCC in cirrhosis seems to be justified in early tumor stages.

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FIVE YEARS EXPERIENCE IN CHEMOEMBOLIZATION OF NON-RESECTABLE PRIMARY HEPATOCELLULAR CARCINOMA (HCC)

K. Schmidt[1], B. Ernst[1], R. Stegemann[1], A. Schüler[2], Klempnauer[3], B. Ringe[3], R. Pichlmayr[3], M. Galanski[4], M. Nagel, and H.J. Schmoll[1].
Departments of [1] Hematology/Oncology and [2]Gastroenterology/Hepatology, [3] Clinic of Abdominal and Transplantation Surgery and [4] Diagnostic Radiology I, Medizinische Hochschule Hannover, FRG.

Introduction: The majority of patients (pts) diagnosed with HCC are not resectabel or transplantable. Encouraged from good results of studies in Japan we startad in 1986 using this therapy to get our own experience. Patients: We embolized 71 pts (10 females / 61 males) with three different therapies (22, 22 and 27 pts) from 1986 to 1992. For tumor staging, we used the UICC (T2 15, T3 10, T4 46 pts) and Okuda criteria (I 42, II 25 and III 8 pts). In all groups, the median age was comparable. Method: Via a femoral artery catheter using Seldinger's technique, a mixture of cytostatic agents and embolization material was introduced to the proper hepatic artery. In Group I, we used cisplatin (50 mg) and epirubicin (50 mg) mixed with lipiodol (5 ml) and a contrast fluid. In Group II we injected lipiodol (5 ml) and then a mixture of Gelfoam powder (500 mg), epirubicin (100 mg) and a contrast medium (10 ml) until the blood flow stopped (2 times in a 3-mos interval, up to 3 times). In Group III, lipiodol (10 ml) with epirubicin (100 mg) was injected, and then the same Gelfoam/epirubicin mixture as in Group II was given (2 times, every 3 mos, up to 3 times). After 5-7 days of embolization and every 6 weeks, we performed a CT-scan control together with clinical and serological tests. Results: Evaluation of the response in Group I showed CR 1, PR 1, SD 2 and PD 18 pts. Group II showed CR 1, PR 8, SD 10 and PD 1 pts (2 early deaths due to the therapy). Group III showed CR 1, PR 8, SD 12 and PD 1 pts (4 early deaths due to cirrhosis; 1 pt could not be followed up). There was a pain of WHO Grade 2 and 3 in Groups II and III. The median survival by Kaplan-Meier after therapy (in brackets: after diagnosis) was 5(19) mos in Group I, 13 (18) mos in Group II, and 13 (18) mos in Group III. The emetic and hematological toxicities were tolerable. Conclusion: The combination of Gelfoam with epirubicin is an effective modality in local therapy of HCC, resulting in a maximal survival of 13 mos. It is a successful palliative therapy in pts with cirrhotic liver.