562 POSTER

HIGH DOSES OF EPIRUBICIN AND 5-FLUOROURACIL WITH OR WITHOUT CISPLATIN IN ADVANCED GASTRIC CANCER

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From Sept. 1991. to Jan. 1995. 80 pts. with advanced gastric cancer entered phase III clinical trial. The aim of the study was to determine activity of high doses of 5-fluorouracil and epirubicin (FE) vs. the same combination + cisplatin (FEP) in that group of pts. Out of 80 pts. 73 were evaluable. The treatment involved in FE arm 120 mg/m^2 of epirubicin i.v. on day 1 and 1000 mg/m^2 in 6-hour infusion of 5-fluorouracil on days 1, 2, 3, 4, 5: in FEP arm the same combination + cisplatin 30 mg/m^2 on days 2.4 was administered. The cycles were repeated after 4 weeks. In FE arm 37 pts. were evaluable with 10 partial and 1 complete remission (29.7%), in FEP arm out of 36 pts. 14 partial and 1 complete remission (41.7%) were observed. Median survival in FE group was 6.3 mos, and in FEP group 8.1 mos. Differences were not statistically significant. Toxicity was tolerable and reversible. Our trial being still under way, the final results will provide a more accurate answer with regard to the value of the two administered protocols.

563 POSTER

EFFICACY OF THE COMBINATION OF ETOPOSIDE (E) AND CISPLATINUM (P) IN THE TREATMENT OF NEUROENDOCRIN DIGESTIVE CARCINOMA (NEC)

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Combination of E and P has shown high response rate in NEC. A pilot study was performed to study the tolerance and efficacy of a new combination ore 120 mg/m^2 day 1 to 3 and P 100 mg/m^2 day 2 every 3 or 4 weeks in the treatment of these patients (pts). 16 pts (male/women: 12/4) have been enrolled. Median age was 46 years. Performance status was <2 in 13 pts. Primary was pancreatic in 10, small bowel in 4, gastric in one and of unknown primary in 1. Metastases were found in 12 pts with liver involved in 8. A poorly differentiated carcinoma was found in 11. A carcinoid secretion was found in 5. Surgery and/or chemotherapy had been performed in 12. 16 pts received 76 cycles (c) (median 5). *Results:* Toxicity: mainly haematological: grade 3 and 4 granulocytopenia in 17 and 18 cycles (2 neutropenic fever), grade 3–4 thrombocytopenia (5 c), grade 4 emesis (7 c), grade 1–2 neurologic (7 c) and grade 1–2 renal (2 c). *Response Rate:* 8/16 PR (50%) with 6/11 in poorly differentiated. NEC, 5 SD and 3 PD. Median duration of response was 7.3 month. Median survival was 10 months. A complete resection was performed in 1. *Conclusion:* Administration of E and P with these doses and schedule result in high response rate with an easily manageable toxicity.

564 POSTER

LITHIUM GAMMOLINOLENATE (LIGLA)- A NOVEL OUTPATIENT TREATMENT FOR NONRESECTABLE PANCREATIC CARCINOMA (PC)

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LiGLA, a lithium salt of an essential fatty acid, has cytotoxicity *in vitro* and *in vivo* against a number of tumour types; a phase II trial has shown median survival of 410 days in patients (pts) with advanced, non-metastatic PC. As part of an ongoing multi-centre randomised phase III study, we have assessed, in a cohort of 6 pts, the feasibility of a short outpatient daily infusion, as compared to the usual inpatient continuous infusion for 10–14 days. All pts had histologically proven non-resectable PC. Karnofsky score >70%, assessable for toxicity & response, & no previous chemotherapy. The maximum period of infusion, via an indwelling. CVC, was 6 hours. Dose escalation was limited by short-lived macroscopic haemoglobinuria (due to an osmotic effect of LiGLA on erythrocytes), which developed at a dose level above 7 g/day. Total dose for each pt (determined by body weight) was 26–84 g. Days of infusion varied from 6 to 16. One pt experienced grade II anaemia. No other toxicities were seen (in particular no renal or Lithium toxicity). This method has a similar toxicity profile to the inpatient infusion. No meaningful comment can be made on efficacy equivalence. Short term infusion should be considered in future trials of this interesting, novel agent. The future development of an ambulatory pump protocol offers a potential home based treatment.

565 POSTER

PHASE II STUDIES WITH EO9 IN BREAST, COLORECTAL, GASTRIC, PANCREATIC AND NSCLC

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EO9 is 8 bioreductive alkylating indoloquinone causing single strand DNA breaks after reduction by DT-diaphorase, with 8 broad spectrum of activity in preclinical studies. In Phase I studies the DLT was proteinuria and renal toxicity at 27 mg/m^2 in the 3-weekly schedule and 15 mg/m^2 in the weekly schedule. The ECTG performed Phase II studies in breast (B), colorectal (C), gastric (G) and pancreatic (P) cancer at the recommended dose of 12 mg/m^2/wk and 1 Phase II in NSCLC (N), randomizing for treatment with 22 mg/m^2 q3wks vs. 12 mg/m^2/wk. Between June 1994 and March 1995 131 patients (pts) were entered in the studies: 22 in B, 28 in C, 20 in G, 24 in P and 39 in N. 1 prior chemotherapy regimen was allowed for B, adjuvant treatment >1 year ago for C. All other tumor types had no prior chemotherapy. The median age of all pts was 59 (range 32–83), median PS 1 (range 0–2). 559 courses (33 of which in the 3 wkly schedule) have been evaluated for toxicity (using NCI-CTC grading). Main toxicities observed were nausea and vomiting (27 and 13% respectively), asthenia (28%), proteinuria (39%), creatinine elevation occurred in 3% of all crs. Proteinuria was more frequent (52%) in the 3-wkly schedule, and 1 episode of a gr.4 creatinine increase occurred in this study arm. Apart from 1 pt with severe fluid retention and renal toxicity with associated symptoms no gr.4 toxicities, and hardly any gr.3 toxicities were seen. So far no responses have been observed in 104 evaluated patients.

566 PUBLICATION

CELL PROLIFERATION IN EXOCRINE PANCREAS OF CARCINOGEN-TREATED RATS AND HAMSTERS

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Cell proliferation in normal pancreatic tissue of saline-treated rats and hamsters and in putative preneoplastic pancreatic tissue of azaserine-treated rats and of N-nitrosobis (2-oxopropyl) amine (BOP)-treated hamsters was determined at 2, 6, 12, 26 and 52 weeks post-treatment. *Rats:* The BrdU Labeling Index (LI) in normal acinar pancreatic cells showed a time-related decrease. The LI in hyperplastic acinar loci was significantly higher than in normal acinar tissue. *Hamsters:* BOP-treatment caused a significant increase in the LI in pancreatic acinar cells. The LI in ductular cells was significantly higher in BOP-treated animals than in saline-treated animals 2 weeks post-treatment, but similar, thereafter. The LI in centroacinar cells was significantly higher in BOP-treated hamsters 2 and 26 weeks post-treatment. Cell proliferation was higher in tubular ductular complexes (lesions with a high potential for malignant transformation) than in cystic ductal complexes (lesions with a low potential to develop to ductular adenocarcinomas). Cell proliferation was highest in borderline lesions (lesions characterized by atypia, desmoplasia and inflammatory cells). It is concluded that determination of cell proliferation provides an easily quantifiable parameter to discriminate between putative preneoplastic lesions with a high or low growth potential, hence with a high or low potential to develop into carcinomas.

567 PUBLICATION

RETROSPECTIVE COMPARISON OF R1 AND R2–R3 GASTRECTOMY FOR CURATIVE GASTRIC CANCER

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The benefit of R1-gastrectomy used in Oulu on 88 pts. (radicality 43.3%) and gastrectomy with extended (R2–R3) lymphadenectomy used in Tartu on 210 patients (pts.) (radicality 60.9%) during the 5-year period from 1983 to 1987 is compared. Although the 5-year survival rates were similar (45.5% in Oulu and 48.1% in Tartu), the comparative data of prognostic factors differed significantly ($P < 0.05$) in T stages, N stages and Borrmann types. The patients in Tartu had higher incidence

of T3–T4 tumors. No patients with T4 or N2–N3 tumors were operated on with curative intent in Oulu. The distribution of expansive: infiltrative Borrmann types was 4:1 (Oulu) and 1:1 (Tartu). Differences in the 5-year survival rates were noticeable ($P < 0.05$) in more advanced stages (T3–T4, N2–N3, Borrmann III–IV types).

We may conclude that these differences can be explained by the more aggressive approach to the gastric cancer surgery in Tartu, specially in patients with advanced tumors. Otherwise the pts. in Oulu are more carefully selected for curative surgery than the pts. in Tartu.

568 PUBLICATION

COMBINED CHEMORADIATION FOR ANAL CANCER: REPORT OF 22 CASES

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From 1988 to 1994 22 patients (pts) with anal cancer, 16 females and 6 males, were treated with concurent CT and RT as definitive therapy. Median age was 64 years (range 39–91). Hystotype was squamous carcinoma in 19 and cloacogenic carcinoma in 3 pts. Distribution per stage was: II 12, IIIA 3, IIIB 3; 4/22 cases were treated after surgical relapse (3 local, 1 inguinal nodal).

CT and RT started the same day. CT, modified from the schedule of Nigro, was: 5-FU 1000 mg/m^2/day for 5 days by continuous, Mitomycin 10–15 mg/m^2 day 1, every 4 weeks. In 11/22 pts 5-FU was administered via a portable infusion pump. RT was delivered 1.8 Gy/day, 5 fractions/week, with a 6 MeV linear accelerator. A median dose of 45 Gy (40–50 Gy) was delivered on the anoperineal volume and the middle and lower pelvis, including bilateral inguinal and external iliac nodes, by opposite anteroposterior portals; after a median split of 10 days, a boost dose was given to the anoperineal region with a direct field by an electron beam of 9–16 MeV, up to a median total dose of 56 Gy (51–63 Gy). The same boost was given to metastatic inguinal nodes.

Nineteen pts completed the treatment and are evaluable for response and toxicity; 3 are still on therapy. Fourteen out of 19 pts received two cycles of CT, 5/19 three or more cycles. Pathologic response was documented in all the pts; pCR was achieved in 100% of cases. With a median follow-up of 19 months (range 5–78), 17/19 pts (89.5%) are free from relapse with mantained anorectal function. Two pts (10.5%) relapsed locally, after 8 and 11 months respectively; in one case abdominoperineal resection was performed as salvage therapy, and the pt is now alive NED; the other pt is receiving further CT.

Eleven pts (58%) had G3-WHO dermatitis; G3–4 sistemic toxicity was uncommon: 2 thrombocytopenia, 1 neutropenia, 1 stomatitis. One pt had an impairment of a previous known angina pectoris. Late toxicity occurred until now in 2 pts, with a vaginal stenosis and a rectal stenosis. No difference in toxicity was observed in pts receiving 5-FU by pump.

The treatment was administered, with a 20% reduction of doses of chemotheraphy, also to elderly pts (4 pts were $\geq$ 75 years), with good tolerance.

Although the period of follow-up is short, our study confirms that concurrent CT-RT is the standard treatment for anal cancer, with relevant but acceptable toxicity; the treatment is feasible and safe also in elderly pts.

569 PUBLICATION

CONTINUOUS FLUOROURACIL INFUSION PLUS ORAL L-LEUCOVORIN AND ORAL ETOPOSIDE IN ADVANCED GASTRIC CANCER

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Gastric carcinoma is considered moderately chemosensitive, but an effective chemotherapy regimen has not yet been found. Encouraging results in terms of activity and tolerability have been reported with a combination of i.v. leucovorin, fluorouracil and etoposide. However, etoposide and fluorouracil have demonstrated a schedule-dependency with high activity for the former when administered orally and for the latter when administered as a continuous infusion. In order to improve clinical results, we tested the activity and feasibility of the following combination: oral L-leucovorin, 5 mg/m^2 days 1–14; oral etoposide, 50 mg/m^2; fluorouracil, given by continuous infusion days 1–14; cycles repeated every 28 days. A total of 20 patients has been enrolled, and 16 are evaluable for response and toxicity (for 4 it is too early). Patient characteristics were as follows: male/female, 11/5; median age, 62 years (range, 49–72); performance status, 0–2; pretreated with surgery/adjuvant chemotherapy, 13/5. Sites of metastasis: 8 liver, 3 lung, 7 lymph nodes, 7 peritoneal carcinomatosis. A total of 52 cycles has been delivered (median/patient, 3 cycles). One complete remission (6%), 6 partial remissions (35%), 4 stabilizations of disease, and 5 progressions have been observed, for an overall response rate of 41%. Median duration of response was 6 months (range, 2–8+) and median time to disease progression was 4 months. No toxic death or grade III–IV toxicity has been observed. Mild or moderate side effects included mucositis (18%), diarrhea (12%) and leukopenia (18%). In conclusion, our preliminary results indicate that the schedule is safe well tolerated and highly effective in advanced gastric cancer.

570 PUBLICATION

THP ADRIAMYCIN (THP): A PALLIATIVE TREATMENT OF LOCAL ADVANCED NON OPERABLE HEPATOCELLULAR CARCINOMA (HCC)

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From 01/91 to 07/94, 20 patients (pts) with non operable HCC and alcoholic liver cirrhosis were treated by THP infusion. The pts were of median age 67 (49–82) years and WHO PS 2 (11) and 3 (9). All tumors were > or = to T3. All liver cirrhosis were Child B or C. *Regimen* was: D1 to D3 THP 20 mg. sqm, 30 mn infusion, Q 4 weeks. Treatment was stopped in cases of appearance of major progression, non manageable toxicity or complete response superior to 6 months. The median number of cycles delivered per pt was 10 (5–26) with a total of 243 cycles.

Toxicity was mainly hematological with neutropenia WHO grade (Gr) III 15%, Gr IV 2%, thrombopenia GrIII 3%, anemia Gr III 1.2%. No cardiac or renal toxicity was observed nor alopecia. Cycles were delayed for 1 week in 4% of cases and a reduction in dose was made in 9%, both for hematological toxicity. There was no septic complication nor hemorrhage.

CT Scan evaluation after 5 cycles showed PD in 7 pts (35%), SD in 5 pts (25%), MR in 1, PR in 4 (20%) and CR In 3 pts (15%). Out of these 3 CR 1 pt had a liver transplantation and died of post-operative complications and the other 2 have a continuing response with 8 and 13 months of follow up after finishing treatment. Ten pts had a high pretreatment alpha foeto protein value. For 5 of these this value decreased, becoming normal in 2 cases, and for the other 5 pts this value increased. Overall median survival was 15 months (5–40). Eleven pts died and 9 are still alive with a median survival of 20 months (9–40).

THP infusion seems to be a good palliative treatment for these poor prognostic HCC with low hematological toxicity, no cardiac toxicity and an objective overall response rate of 35%

571 PUBLICATION

EXTERNAL RADIOTHERAPY AND INTRALUMINAL BRACHYTHERAPY IN ADVANCED STAGES ESOPHAGAL CARCINOMA

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The treatment for patients with advanced stages esophagal carcinoma should be aimed at maintenance of local control by means of saving esophageal passage, improving disphagia and oral nutrition and preventing aspiration pnömonia as these sorts of complications are fatal. In this study, it was performed 15–16 Gy high dose rate intraluminal brachytherapy in 3 fraction preceded by 46–48 Gy external radiotherapy to 14 advanced stage inoperable patient in order not to exceed tolerable doses of the neighbouring tissues while maintaining efficient local control by radiation. Seven patients received neoadjuan chemotherapy. Patients were assessed symptomatically, endoscopically and radiologically every 3 months after completion of treatment. Before treatment 6 patients could not take and 8 patients received only fluid food. We achieved symptomatic palliation in all of the patients. Endoscopically it was founded no macroscobic tumor in 6 patients, 1–2 cm tumor in 4 patients and bigger than 2 cm in 4 patients 3 months after treatment. Seven patients had distant metastasis. Survival was between 5–18 (mean 10 months). We did not observe radiation ulcer. External radiotherapy plus intraluminal brachytherapy is effective and safe for obtaining local control in advanced disease esophagal carcinoma.