570 PUBLICATION

Preoperative chemo-radiotherapy (CHRT) in esophageal carcinoma (EC): response, toxicity and survival analysis

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Purpose: To evaluate preoperative ChRT in resectable localized EC. Patients (pts) treated with this combined modality in our institution were retrospectively reviewed.

Patients and Methods: From Jan 93 to Aug 98, 33 pts were treated, 32 M/1 F. Mean age 53 y (range 38–69). PS <= 1. Squamous cell: 32, adenocarcinoma 1. All of them were thoracic cancers: 3 upper 3rd, 24 middle 3rd and 6 distal 3rd. Preoperative work-up consisted of esophagoscopy, barium swallow, bronchoscopy, thoraco-abdominal CT scan and pulmonary function. Mean tumour length: 6.8 cm (range 5–12). N0: 25, N1: 8. Treatment protocol: two courses of CDDP 100 mg/m^2 d1 and 5FU 1000 mg/m^2 d1–5 on 1st and 6th wks, with radiotherapy (35 Gy) from 2nd to 5th wks, followed by esophagectomy on 10th wk.

Results: Thirty pts (91%) received full-projected preoperative treatment; 2 pts only one cycle of QT, and one pt 30 Gy. ChRT toxicity: 1 episode (ep) of neutropenia gr 3–4; 1 ep. thrombopenia gr 3–4; 11 ep. emesis gr 2 and 1 ep. gr 3; 3 ep mucositis gr 2–3. Twenty-seven pts (82%) were operated, 25 (76%) with curative resections. Two pts of 27 (7.5%) died of surgical complications. There were 6/33 (18%) pathological complete responses with ChRT and 21/33 (64%) partial responses. Median survival for all pts was 13 months and 3 years survival 25%. Median actuarial disease free survival was 13 months.

Conclusions: Preoperative ChRT is a well tolerated treatment. Pathological responses are seen frequently and surgical morbi-mortality is comparable to other series without preoperative approach. ChRT may improve prognosis of these pts by controlling local and distant disease, previous to definitive treatment. Marginally operable tumours may be resected in responding pts.

571 PUBLICATION

Postoperative radiotherapy for gastric cancer

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Purpose: Surgery is considered as a primary treatment for locally advanced gastric cancer (LAGC). To improve local control and survival postoperative radiotherapy (RT) is investigated.

Methods: From 1986 to 1995 85 LAGC consecutive pts. were irradiated using high energy photons after resection, of whom D2 lymphadenectomy was performed in 10.5%, D1 in 76.5%, D0 in 13% of pts. Age: 30–77 yrs, mean-55 yrs, women: 26, men: 59. In 61 pts. RT was as adjuvant modality (R0 resection in pT3/T4 or pN1/N2 lesions), in 24 pts. it was given after R1 resection. No chemotherapy was given pre- or postoperatiely. RT to total dose of 46–60 Gy (median: 50.6 Gy) in 1.8–2.0 Gy per fraction was delivered.

Results: RT was well tolerated with no more than G2 acute toxicity according to RTOG/EORTC. The 5-yr overall actuarial survival (OS) rate was 37.5% (median survival: 21 mo). The disease-free survival rate (DFS) was 27.8% (median DFS: 16 mo). Independent survival related prognostic factors established using Cox multivariate analysis appeared to be: pT and pN. Neither presence of microscopic residual disease (R1 resection) nor the type of lymph node dissection (D) did show prognostic influence on survival after RT. The subset analysis showed best overall survival rates (OS-79% at 5-year) for pts. with pN0, independent from pT status. Combination of the worst prognostic factors: pT3/T4 and pN+ lead to survival rate of only 8%. Also for DFS – pN was the most important prognostic factor.

Conclusion: Postoperative external beam RT for LAGC does not influence OS and DFS in pts. treated primarily with non-optimal surgery (R0, R1 resection, D0, D1 lymphadenectomy). The potential benefit of RT may exist only for pN0 pts. after R1 resection, who cannot be reoperated.

572 PUBLICATION

Taxotere–5FU Leucovorin (TFL) in advanced gastric carcinoma: A HeCOG phase II study

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Purpose: Taxotere has shown significant activity in advanced gastric carcinoma (as single agent RR: 23% and in combination with cisplatin RR: 58%). The purpose of this study was to assess the efficacy and toxicity of the TFL combination as first line chemotherapy in patients with advanced gastric carcinoma.

Methods: From Jan 1997 to Jan 1999 27 previously untreated parients (11 female and 18 male) with a median age of 63 (37 ± 76) and performance status 1 (0 ± 2) were enrolled. The site of metastatic disease was: locoregional (15 pts), liver (14 pts), lymph-nodes (5 pts), ascites (3 pts), lung (2 pts) and bones (1 pts). Chemotherapy consisted of Docetaxel (75 mg/m^2), 5 FU (500 mg/m^2) and Leucovorin (300 mg/m^2) on day 1 every 3 weeks.

Results: So far 104 cycles of chemotherapy were administered and up to now 25 patients were evaluated for toxicity and 19 for response. Objective responses were noted in 5 (26%) patients (1 CR, 4 PR), stable disease in 9 (48%) patients and progressive disease in 5 (26%) patients. Median duration of response was 10.4 (1.7 ± 11.77) months. Grade 3 and 4 toxicity was: neutropenia 31% of pts (but only 1 case of febrile neutropenia), thrombopenia 3.5% of pts, diarrea 10% of pts and mucocitis 3.5% of pts. There was one toxic death (febrile neutropenia).

Conclusion: TFL combination is an active regimen in patients with advanced gastric carcinoma, with acceptable toxicity. The median survival of the patients was comparable to established regimens.

573 PUBLICATION

Modified ECF in the treatment of advanced oesophago-gastric cancer – An active regimen without the need for central venous catheter mediated therapy

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Introduction: ECF with prolonged infusional 5FU is an established active regimen for the treatment of advanced oesophago-gastric cancer. This treatment requires therapy through a central venous catheter. We reviewed our experience of a modified ECF regimen ("ECbolusF") for use in patients (pts) who refused continuous infusional therapy or who were considered unsuitable for such treatment.

Methods: A retrospective review of all pts with advanced oesophago-gastric cancer (24 oesophageal, 16 gastric, and 6 gastro-oesophageal) treated with ECbolusF between 6/94 and 6/98 was undertaken. 46 pts (34 male), median age 67 years (range 36–80) were treated with epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, and 5-FU administered as a 6-hour infusion (bolus F) 600 mg/m^2 q 21 days. 26 pts had metastatic disease and 20 locally advanced disease at treatment commencement. The median number of cycles administered was 3 (range 1–9).

Results: 34 pts were evaluable for response and the overall response rate was 38%. A further 5 (15%) pts demonstrated stable disease. The median survival of all treated pts was 4.6 months. However, the median survival of the 37 pts who received at least 2 cycles of therapy was 6.9 months. ECbolusF was well tolerated with the only grade 4 toxicity recorded being diarrhoea (1 pt), and grade 3 toxicity of alopecia (9 pts), anaemia (2 pts), leucopenia (2 pts), and diarrhoea (1 pt). There were no treatment related deaths.

Conclusion: ECbolusF has demonstrated significant activity and was well tolerated in a patient group with biases that favoured a poor outcome. Evaluation of chemotherapy regimens that obviate the need for central venous catheter mediated therapy in advanced gastro-oesophageal cancer are recommended.

574 PUBLICATION

Taxotere (T) in advanced solid tumors (AST) other than advanced breast cancer resistant to chemotherapy (CH) or hormonotherapy (H)

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Introduction: Patients (pts) with advanced disease resistant to previous CH or H were treated with T as single agent and evaluable for response (R)

and toxicity (T). Pts and Methods: 20 pts, M/F = 10/10; PS 0–2; Median age 64y (40–75). Types of tumors: 5 pts Advanced Pancreatic Cancer (APC) and 2 pts Advanced Gastric Cancer (AGC), both resistant to FAM; 5 pts Advanced Head & Neck Cancer (AHNC) resistant to 5-FU-CDDP; 3 pts Advanced Ovarian Cancer (AOC) resistant to Taxol and 5 pts Advanced Prostate Hormonotherapy Resistant Cancer (APHRC). Treatment: T 100 mg/m^2, 1 hr. infusion every 21 days, until disease progression. Response: OR (CR + PR): 7/20 (35%) (CR: 1 AOC; PR: 2 APC, 1 AHNC, 2 AOC, 1 APHRC); SD: 10/20 (50%) (2 APC, 1 AGC, 4 AHNC, 3 APHRC); PD3/20 (15%). Toxicity: Neutropenia G3/4: 6/20 p (30%) and G2: 7/20 p (35%); 12/20 p (60%) required CSF.

Conclusion: T is very active as single agent in Advanced and Resistant Tumors (APC, AOC, APHRC and AHNC). Neutropenia is important but reversible.

575 PUBLICATION

Curative and palliative therapy of pancreatic cancer: A retrospective analysis

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Background: Pancreatic cancer is responsible for 3% of all tumors and 10% of the digestive tumors. The 5-year survival rate is only 1–3%, in which the first diagnosis 80% of the patients are nonresectable primary.

Methods: We report about the treatment of 177 patients (85 women, 92 men) with pancreatic cancer from 1993–1998. The hstological types of carcinoma were: 147 ductal adenocarcinoma, 10 carcinoma of the papilla, 5 endocrine tumors and 1 epithelioma. In 67.2%, the tumor was localized in the head, 12.4% in corpus/tail and in 5.5% in the papille. 14 patients were without secure histological diagnosis, and definitive location of the tumor was unknown. At the time the tumor was first diagnosised 17.3% were lymph node negative. 17.3% were Stage III and 65.3% of the patients were Stage IV.

Results: A primary surgical curative treatment was performend: 54 Whipple's operation, 5 leftside resection, 1 transduodenale extirpation of the papilla with a hospital lethality of 5.5% and a 30-day lethality of 1.8%. 82 patients had a histologically proven nonresectable primary (primary palliative operation). 26 patients were treated with locoregional chemotherapy (aortic stop flow; i.a. truncus coeliacus), 53 patients with a primary chemotherapy (gemcitabine and gemcitabine/docetaxel). The median survival time was 6.9 month in this group, patients with locoregional therapy it was 4–4.5 months and in the group of the patients who underwent complete surgical resection it was fuond to be 14.8 month.

Conclusion: A possibility to improve the survival time of patients with pancreatic cancer is the early first diagnosis and the improvement ofcombinations mutimodal therapy options.

576 PUBLICATION

Improvement of efficacy of Gemcitabine (G) on xenografts of human pancreatic carcinomas in nude mice by combination with Mitomycin-C (M-C)

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Stimulated by clinical data (R. Klapdor et al, J. Cancer Res. Clin. Oncol. 124, 1998, R11) we investigated the antitumor efficacy of Gemcitabine in xenografts of human pancreatic carcinomas established in nude mice in comparison to a combination of Gemcitabine (G) + Mitomycin-C (M-C).

Methods: 5 different human panceratic carcinoma xenografts established in our own lab were treated with 20, 40, 80, 160 mg/kg b.w. G resp., and in a second study with a combination of 30, 80 and 130 mg/b.w. G + 1.9 mg/kg M-C and 120 mg/kg b.w. G + 0.5, 1.1 and 1.9 mg/b.w. M-C resp., given weekly for 3–5 weeks by i.p. application. Each group comprised 5–6 nude mice. Treatment was started at tumor sizes between 200–400 ccm.

Results: G showed a dose dependent tumor growth inhibition in 2/5 xenografts (2/5 partial responses after 3 weeks treatment with 160 mg/kg b.w.). Combination with M-C (120 mg/kg b.w. G + 1.9 mg/kg M-C) resulted in 4/5 partial remission and 1/5 stable diseases. In the nude mice bearing xenografts resistant against G monotherapy also a subsequent treatment with a combination of G + M-C like a second line therapy induced partial responses. Combined treatment did not affect body weigth of the nude mice more than G alone. Also in an additional experimental study in nude mice bearing xenografts of a human gastric carcinoma combined treatment with G + M-C resulted in a significant tumor growth inhibition with PR after 3 weeks, as also found for 5-FU (110 mg/kg b.w. weekly i.p.) and Oxaliplatin (15 mg/kg b.w. weekly i.p.).

Conclusions: a) Combined treatment of exocrine pancreatic cancer with a combination of G + M-C seems to be more effective than G alone. b) This combination might also be of clinical relevance in patients suffering from other tumor entities, at least in single cases.

577 PUBLICATION

Docetaxel as salvage chemotherapy in advanced gastric cancer patients (AGC): A phase II study of the Southern Italy oncology group (GOIM)

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Purpose: Gastric cancer is considered the most responsive of all digestive tract cancers, and various combinations of cytostatic agents (generally containing 5-fluorouracil and anthracyclines) have been employed in advanced disease. After first-line failure, no standard salvage treatment was identified and then new drugs were explored. In particular, docetaxel showed considerable activity in patients with AGC (Sulkes, Br. J. Cancer 1994; Einzig, Medical Onco 1996). Following these results, from November 1998, patients with AGC previously treated with first-line chemotherapy were enrolled in this phase II multicentric trial.

Methods: Patients received Docetaxel 100 mg/m^2 as a 1-hr infusion, every 3 weeks. Up to now 11 pts were enrolled in the study. All pts were pretreated with 5-Fluorouracil and Epimbicin containing regimens. The main characteristics of the entered pts were as follows: sex (M/F): 9/2; median age 65 yr (range: 22–69); median ECOG PS 1; sites of disease: liver 6, lymphnodes 4, relapse 2, other 5.

Results: Seven patients are actually evaluable for response and toxicity: Two objective responses, 2 stable disease and 3 progressive disease with an overall response rate of 29%. With regard to toxicity (WHO criteria) 2 patients showed grade 3–4 leukopenia. No other grade 3–4 toxicities were observed.

Conclusion: The study is still ongoing. These preliminary results suggest thatdocetaxel is active in previously treated patients with AGC.

578 PUBLICATION

A prospective study of MRI in the staging, and response assessment of patients treated with chemo-radiation (CRT)

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Purpose: To prospectively use the recognised soft tissue contrast sensitivity of MR in the staging, and assessment of response to treatment following CRT, in patients with anal cancer.

Method: Ten patients entered prospectively into UKCCR Anal Cancer Trials employing chemo-radiation were assessed by sequential MRI. The technique included small field of view axial and coronal T2 and STIR images. These images were obtained pre-treatment, 3–4 weeks after completion of chemo-radiation phase I and prior to phase II, 1 month and 6 months after completion of all treatment. Clinical evaluation was performed at each MR assessment.

Results: By MR criteria, staging was allocated as follows T1-1, T2-2, T3-4 and T4 – 3 patients; 2 patients had N2 disease. Response status, as assessed by MR is summarised below.

Assessment time point	MR Response			
	CR	PR	PD	OTHER
Post Ph I CRT	3	7	–	–
1 Month post ph II	8	–	1	1
6 Months post ph 2	7	–	–	3

There was no instance where clinical examination conflicted with the MR assessment of response. The one instance of PD was confirmed clinically and histologically.

Conclusion: MRI provides detailed anatomical information on tumour extent leading to confident non surgical TN staging. The use of MR with its inherent soft-tissue contrast has recorded detailed changes during, and following, CRT. This response assessment was in keeping with clinical examination.