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Perioperative chemotherapy in operable gastric and lower oesophageal cancer: a randomised, controlled trial of the UK NCRI Upper GI Clinical Studies Group (the MAGIC trial, ISRCTN 93793971)

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Background: Epirubicin, cisplatin and infused 5-FU (ECF) has been shown to confer a significant benefit in advanced oesophagogastric cancer, particularly locally advanced disease. This trial was designed to determine whether this effect can be translated into a survival advantage in operable disease.

Material and Methods: Patients with adenocarcinoma of the stomach, oesophagogastric junction or lower oesophagus suitable for curative resection were randomised to receive perioperative chemotherapy (CSC arm) or surgery alone (S arm). In the CSC arm, chemotherapy consisted of three pre-operative and three post-operative cycles, 3 weeks apart, of epirubicin 50mg/m2 IV bolus, cisplatin 60mg/m2 infusion and 5-FU 200mg/m2/day continuous infusion.

Results: Between 1994 and 2002, 503 patients (250 CSC, 253 S) were randomised; 74% were gastric, 15% oesophago-gastric junction and 11% oesophageal cancers. In the CSC and S groups respectively, median age (range) was 62 (29-85) and 62 (23-81) years; 82% and 75% were male; and 68% and 68% had WHO performance status 0. Maximum tumour diameter at entry was similar for both arms: median diameter (interquartile range) was 5 (3-7) cm for CSC patients and 5 (3-7) cm for S patients.

In the CSC arm, 88% of patients completed pre-operative chemotherapy, 57% commenced post-operative chemotherapy and 43% completed all 6 cycles. The main reasons for failing to start post-operative chemotherapy were death, progression, patient request and post-operative complications.

Median time to surgery from randomisation was 99 days in the CSC arm and 14 days in the S arm. Resection was considered curative in 79% CSC compared with 69% S patients (p=0.02, Chi-squared test). Post-operative complications were similar (CSC 47%, S 45%) as were deaths within 30 days (CSC 6%, S 6%) and median time to discharge from hospital following surgery (CSC 13 days, S 13 days).

Maximum diameter of the resected tumour was smaller in the CSC arm: median diameter (interquartile range) was 3 (2-6) cm for CSC patients and 5 (3-8) cm for S patients (p<0.001, Mann-Whitney U test). For gastric and junctional patients, pathological staging demonstrated 51% CSC were T1/T2 compared with 36% S (p=0.01, Chi-squared test) and 80% CSC were N0/N1 compared with 71% S (p=0.16, Chi-squared test).

Progression-free survival was significantly better in the CSC arm (Hazard Ratio [HR] = 0.70, 95% Confidence Interval [CI] 0.56 – 0.88, p = 0.002); there was a trend towards improved overall survival (HR = 0.80, 95% 0.63 – 1.01, p = 0.06). Overall survival at 2 years was 48% in the CSC arm and 40% in the S arm.

Conclusions: Perioperative chemotherapy improves progression-free survival, reduces tumour size and increases resectability in operable gastric and lower oesophageal cancer. There is a trend towards improved survival that does not at present reach conventional levels of significance.

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Randomized phase II trial of LV5FU2, LV5FU2-cisplatinum or LV5FU2-irinotecan in patients (pts) with metastatic gastric or cardial adenocarcinoma (MGA): final results of study FFCD 9803.

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Although ECF (epirubicin-cisplatinum-infusional 5FU) is considered a standard chemotherapy in the treatment of pts with MGA, it is demanding and often toxic. The contribution of cisplatinum (P) remains controversial whereas the activity of irinotecan (I) is promising. Our purpose was to determine the efficacy and the tolerance of LV5FU2 alone or with P or I in 1st line MGA and to define the best arm for a phase III study.

Methods: Pts with histologically proven MGA, and measurable disease, age < 75 years, WHO performance status (PS) < 3, not pretreated and without linitis were randomized between: Arm A: LV5FU2 (folinic acid 200 mg/m* IV over 2 hours followed by 5FU 400 mg/m * IV bolus then 600 mg/m* CI of 5FU over 22 hours D1 and D2, fortnightly); Arm B: LV5FU2 + P 50 mg/m* IV over 1 hour D1 or D2; Arm C: LV5FU2 + I 180 mg/m* IV over 2 hours on D1. Efficacy was determined every 8 weeks.

Results: 136 pts were included, 2 pts were ineligible. For 134 analyzed pts: PS 0-1/2: 76/24%; gastric/cardial tumoral site: 69/31%. Arms A (45 pts), B (44 pts) and C (45 pts) were well balanced in terms of pretreatment characteristics. Respective median number of cycles were 7 [1-20], 7 [1-18], and 10 [1-25]. Treatment was stopped for toxicity for 0% (arm A), 14% (arm B) and 4% (arm C) pts. Main gr 3-4 toxicities were (%pts): neutropenia: 11/59/40; anemia:16/30/16; mucitis:4/2/7; nausea/vomiting:13/23/7; diarrhea:2/2/22. Two toxic deaths occurred (1 in arms A and B). The ORR confirmed by an independent expert panel was: arm A: 13% (6/45), B: 27% (12/44), C: 40% (18/45). Median progression free survival and overall survival were [95% CI]: arm A: 3.2 [1.8-4.6] and 6.8 [2.6-11.1] months; B: 4.9 [3.5-6.3] and 9.5 [6.9-12.2] months; C: 6.9 [5.5-8.3] and 11.3 [9.3-13.3] months.

Conclusions: LV5FU2 is considered to have insufficient efficacy. The toxicity profile and the efficacy of the LV5FU2-I combination are highly encouraging and will be assessed in a phase III study. Supported by Aventis, Baxter and the Association pour la Recherche sur le Cancer (ARC).

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Gemcitabine versus GEMOX (Gemcitabine + Oxaliplatin) in non resectable pancreatic adenocarcinoma: a GERCOR /GISCAD Intergroup Phase III

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Gemcitabine according to Burris study (1 g/m^2 in a 30 min infusion weekly) remains the reference treatment of non resectable pancreatic adenocarcinoma. The combination of gemcitabine 1 g/m^2 as a 100 min infusion (10 mg/m^2/mn) D1 and oxaliplatin 100 mg/m^2 in 2h infusion D2 (GEMOX) demonstrated promising results in a multicenter phase II study (Louvet et al, JCO 2002). This intergroup randomised study was designed to compare gemcitabine (according to Burris) to GEMOX regimen. Patients were stratified according to center, performance status and type of disease (locally-advanced (LA) or metastatic (M)). The study was design to demonstrate a 2-month increase in median survival (6 to 8 months). 326 patients have been enrolled; 13 were non eligible, 156 were allocated to Gem arm and 157 to Gemox arm.

Patients characteristics (Gem / GEMOX): Male: 53% / 60%; Mean age: 60.1 yrs / 61.3 yrs; LA: 30% / 32%; PS 2: 18% / 17%; tumor located in the pancreatic head: 50% / 54%; liver met: 59% / 58%

Gr 3-4 toxicity (per pts, Gem / Gemox): neutrophils: 26.3% / 18.5%; platelets: 3.8% / 12.8%; hemoglobin: 9.6% / 6.4%; nausea-vomiting: 3.2% / 8.9%; diarrhea: 1.3% / 5.1%; neuropathy: 0% / 15.3%; alopecia (gr 2): 1.9% / 4.5%; any toxicity grade 3-4: 37.9% / 47.8% (p = 0.15)

Efficacy: Response rate (investigator assessement): 16.1% / 25.8% (p = 0.03); Clinical benefit: 28.3% / 39.2% (p = 0.05); PFS (median): 16 w / 25w (p = 0.05)

Gemox is significantly superior to Gem in terms of response rate, clinical benefit and progression-free survival. A longer follow-up is needed to obtain final data on overall survival.