6509 POSTER DISCUSSION

5-FU/l-LV (RPMI) versus S-1 as first-line therapy in patients with advanced gastric cancer: a randomized phase III non-inferiority trial. (ISO-5FU10 Study Group trial)

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Background: The phase III study (JCOG9912) showed a clinical benefit and non-inferiority of oral S-1 (5-FU based medicine) compared to intravenous 5-FU for advanced gastric cancer (AGC). On the other hands, 5-FU combined with LV is expected to enhance the therapeutic efficacy. There was no randomized trial to compare 5-FU/l-LV (RPMI) with S-1. We planned this phase III trial to investigate the non-inferiority of RPMI in comparison with S-1 for patients with AGC.
Methods: The primary endpoint was overall survival, and the secondary endpoints were response rate, progression free survival, time to treatment failure, safety and QOL. Eligibility criteria included histologically proven adenocarcinoma of the stomach, unresectable or recurrent with measurable lesion, age 20−77 and PS 0−2. RPMI (l-LV 250 mg/m^2 2 h-iv and 5-FU 600 mg/m^2 iv bolus) was given intravenously once weekly followed by a 2-week rest period, within a 8-week cycle. S-1 (40−60 mg depending on pts body surface area) was given orally twice daily for the first 4-week of a 6-week cycle.
Results: 191 pts were enrolled from 60 institutes from May 2002 to August 2006, and were randomized. 177 of the 191 pts were eligible to evaluate which were 89 in RPMI arm and 88 in S-1 arm. The two arms were well balanced (Arms RPMI/S-1): median age 65.0/63.0 years, unresectable gastric cancer 78/75 pts, metastatic disease 65/68 pts. Median overall survivals (95%CI) were 10.3 (8.1−12.9) months in RPMI arm and 8.3 (6.9−10.4) months in S-1 arm, and the hazard ratio of RPMI for S-1 was 0.84 (95%CI: 0.60−1.18). No significant differences in survival time between RPMI and S-1 was observed. Response rate are equal in two arms (p = 0.208: RPMI: 23.6%, S-1: 29.5%). Median progression free survival (95%CI) were 4.0 months (3.2−8.5) in RPMI arm and 3.5 months (2.8−5.1) in S-1 arm, and the hazard ratio was 0.76 (95%CI: 0.55−1.06). Median time to treatment failure (95%CI) were 3.0 months (2.0−3.7) in RPMI arm and 2.8 months (2.5−3.3) in S-1 arm, and the hazard ratio was 0.95 (95%CI: 0.69−1.31). No significant differences in safety and QOL were observed between two arms.
Conclusions: RPMI showed significant non-inferiority for overall survival and progression free survival versus S-1 in the first-line treatment of AGC. RPMI is an effective alternative to S-1.

6510 POSTER DISCUSSION

Sequential therapy with FOLFIRI followed by docetaxel plus cisplatin: a promising adjuvant chemotherapy in gastric adenocarcinoma. 5-year follow-up results of the I.T.M.O. Group study

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Background: Adjuvant therapy in the gastric cancer is in continuous evaluation in order to find the optimal treatment schedule. In a previous report the I.T.M.O. Group documented the feasibility of a sequential therapy including the irinotecan (CPT-11) with fluorouracil (FU) and docetaxel plus cisplatin (Oncology, 71;2006). This regimen was chosen to compare FU/leucovorin in ongoing Italian Intergroup trial (ITACA-S) in which more than 1000 patients have been recruited up to day. We present the efficacy analysis of the ITMO study after 5-year follow-up. This multicenter phase III trial started in 2002 with aim of comparing sequential therapy with mytomicin C in adjuvant setting.
Material and Methods: 169 pts with histologically confirmed adenocarcinoma of the stomach or of gastroesophageal junction radically resected (pT3/4 or with nodal involvement) were enrolled; pts were randomized to receive sequential polychemotherapy consisting of FOLFIRI regimens (CPT 11 180 mg/mq d1 + leucovorin 100 mg/mq d1−2 + FU 400 mg/mq bolus d1,2 + FU 600 mg/mq c.i. 22 h d1,2) for four cycles followed by three weekly combination of docetaxel (85 mg/mq d1) plus cisplatin (75 mg/mq d1) for three cycles (arm A) or monochemotherapy with mytomicin C (8 mg/mq d1,2 q42) for four cycles (arm B). Survival curves were calculated by Kaplan-Meier method and the long rank test was used to compare the DSF (primary study end-point) and OS data of the two trial arms.
Results: Out 166 evaluable pts, 85 entered arm A and 81 arm B. After a median follow-up of 66 months (IQ range 53−79), 64 pts relapsed, 27 in arm A (32%) and 37 in arm B (46%). A significant difference in DFS at 5-years was achieved: 66% in arm A and 50% in arm B (p = 0.0579). OS was more favourable in arm A, with an estimated probability of 67% in arm A and in 53% in arm B (p = 0.16).
Conclusions: These data confirms overall survival probability of more than 50% at 5 years, as obtained by other Italian trials. Sequential therapy with FOLFIRI for four cycles followed by three cycles docetaxel plus cisplatin is a feasible and effective regimen. Mentioned data represents a strong rational for ongoing ITACA-S trial, which will be soon concluded.

6511 POSTER DISCUSSION

Human epidermal growth factor receptor 2 (HER2) in gastric cancer (GC): results of the ToGA trial screening programme and recommendations for HER2 testing

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Background: ToGA (BO18255; F Hoffmann-La Roche) is the first randomised, Phase III trial evaluating the addition of trastuzumab (Herceptin®) to chemotherapy in HER2-positive advanced GC. HER2-screening results from ToGA have been published previously with an overall HER2-positivity rate of 22.1%. We report on the correlation of HER2 status analysed by immunohistochemistry (IHC) and fluorescence *in situ* hybridisation (FISH) with clinical outcome in the respective subgroups. Based on these results, a HER2-testing algorithm for GC will be recommended. Furthermore, the aspects of polysomy and gene amplification will be discussed in the context of clinical efficacy.
Materials and Methods: Central screening of advanced GC tumour samples was performed in parallel by IHC (HercepTest™) using modified scoring (Hofmann et al. *Histopathology* 2008;52:797–805) and FISH (pharmDx™). Patients were considered eligible for trial entry if the tumour was IHC 3+ and/or FISH positive.
Results: A total of 3807 patients in 24 countries were screened, of whom 810 showed HER2 overexpression/amplification fulfilling the ToGA entry criteria. No difference in HER2-positivity rates was observed between Europe and Asia (23.6% vs 23.5%). HER2-positivity rates differed according to tumour location and type: rates were higher in gastro-oesophageal junction (GEJ) than stomach cancer (33.2% vs 20.9%; p < 0.001) and in intestinal than diffuse/mixed cancer (32.2% vs 6.1%/20.4%; p < 0.001). Above-average HER2-positivity rates were observed in countries with the highest GEJ:stomach cancer ratios (France 0.56 [HER2 positivity 26.9%]; Germany 0.53 [23.7%]; UK 0.33 [25.8%]) and intestinal:diffuse cancer ratios (UK 3.4 [HER2 positivity 25.8%]; Australia 2.6 [32.8%]; Japan 2.8 [28.1%]). Concordance between IHC and FISH using the modified HER2-scoring system was 87.2%. Unlike in breast cancer, where most IHC 0/1 samples are FISH negative, the proportion of IHC 0/1 samples testing FISH positive in ToGA was almost as high as IHC 2+/FISH-positive samples (23% vs 26%).
Conclusions: In ToGA, the overall HER2-positivity rate in advanced GC was 22.1%. Differences in HER2-positivity rates between countries are likely due to variations in tumour location and histological subtype. The clinical significance of HER2 IHC score (0, 1+, 2+, 3+) and FISH ratio will be evaluated and the HER2-testing algorithm recommended that may lead to further refining of HER2 positivity.