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Capecitabine (X) and etoposide (E) for patients (pts) with locally advanced or metastatic gastric cancer: a Mexican Oncology Study Group phase II trial

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Background: Palliative chemotherapy is the mainstay of treatment for >60% for pts with non-operable/metastatic gastric cancer and for the 80% of cases with recurrent disease after surgery. Response rates for combined chemotherapy range from 0–70%, but half of the pts die within 1 year. Toxicity of the most popular schedules remains high. Therefore, schedules for elderly and poor performance pts are needed. The ELF combination was designed with this aim and produced good results: 53% response rate and 17-month survival in locally advanced responders. X monotherapy is active in the general gastric cancer population with response rates of approximately 30%. This study was conduced to evaluate the XE combination in a poor-prognosis population.
Materials and methods: pts with locally advanced non-resectable gastric cancer or recurrent disease, without previous systemic treatment, were treated with X 1000 mg/m^2 twice daily on days 1–14 + E 120 mg/m^2/day x 3 days, every 3 weeks. Primary objective was response rate (by RECIST criteria) and secondary aims were safety, quality of life, PFS and OS.
Results: Baseline characteristics of the 65 pts enrolled were: male/female (35/30); median age 53 years; ECOG PS 0/1/2 (25%/58%/17%). Main metastatic sites were: stomach (66%), lymph nodes (21%), liver (9%), other (20%). Median number of delivered cycles: 5 (range 1–14). Safety is shown in the table.

% of pts	All grades	Grade 3/4
Anaemia	78	3
Neutropenia	31	14
Thrombocytopenia	8	0
Hand–foot syndrome	45	2
Mucositis	45	0
Diarrhoea	11	0
Vomiting	21	4

Overall response rate was 21% (including 4 pts with CR, all with single site tumour activity), with stable disease in 21% of pts, disease progression in 31%, and ongoing treatment in 27% of pts. Median survival time is 13 months (95% CI, 7–20 months). Quality of life was measured during each cycle: global health status improved to double the basal score at cycle 3 and remained at this level until cycle 5 ($p = 0.006$); treatment reduced fatigue to half that observed at baseline and remained low until cycle 5 ($p = 0.015$); pts perception of nausea/vomiting disappeared from cycle 2 until cycle 5 ($p = 0.05$) and none of the cycles were worse than the baseline level; other symptom scales did not change over time. Physical, emotional ($p = 0.014$) and social functioning improved from cycle 2 onwards.
Conclusions: treatment was well tolerated, dose intensity maintained, quality of life improved in almost all domains and median survival was comparable with that observed with more intensive combination regimens in pts with a less-poor prognosis.

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Gemcitabine plus oxaliplatin (GEMOX) in advanced hepatocellular carcinoma (HCC): results of a phase II study

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Background: New therapies are clearly needed to improve the prognosis of patients (pts) with advanced HCC. The rationale to develop the gemcitabine/oxaliplatin combination in HCC is based on: (i) the synergy between these two drugs, (ii) the clinical activity of Gemcitabine alone and the FOLFOX regimen in HCC according to preliminary phase II results, (iii) the lack of renal or hepatic toxicity of oxaliplatin in cirrhotic pts. Recently, we conducted a pilot study to evaluate two distinct bimonthly schedules of gemcitabine plus oxaliplatin in advanced HCC. We have therefore selected the most promising schedule to perform a phase II trial in non pre-treated advanced HCC patients.
Methods: 34 pts with non pre-treated advanced HCC were prospectively enrolled. They received gemcitabine 1000 mg/m^2 d1 and oxaliplatin 100 mg/m^2 d2 (GEMOX). Treatment was repeated every two weeks until disease progression or limiting toxicity. Eligibility criteria were: pathologically proven advanced HCC or alpha-fetoprotein (AFP) levels over 250 ng/ml associated with a radiological liver tumor, PS (ECOG) 0–2, age >18, measurable disease, adequate hematological and renal functions, compensated Child score <9, and written informed consent.
Results: Thirty two patients are currently evaluable for efficacy and 33 for toxicity. Patient's characteristics, were mean age: 58 (37–82), sex (M/F): 28/6, PS (0/1/2): 8/19/7. 271 cycles of treatment were performed. No toxic death occurred. Hematological grade 3–4 toxicities consisted in thrombocytopenia (27%), anemia (9%) and neutropenia (24%), with 2 febrile neutropenias and no bleeding event. Grade 1, 2 and 3 neurotoxicity occurred in 19, 7 and 3 pts, respectively. No other grade 3–4 toxicity was observed. Five objective and 6 minor responses and 15 stable diseases were observed. Leading to a disease control rate of 77%. One pt have had a curative resection following GEMOX treatment.
Conclusion: gemcitabine plus oxaliplatin seems to be a relatively active regimen with manageable toxicity in non pre-treated cirrhotic patients with advanced HCC.

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Identification of hedgehog-related downstream genes in pancreatic cancer cell

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Background: Several types of cancer have been linked to a disruption of the hedgehog (Hh) signaling pathway, which is crucial to the normal development of many organs. The Hh signaling might also be an important mediator in the development and maintenance of human pancreatic cancer. However, little is known about the function of activated Hh signal and the Hh signaling-related downstream genes in pancreatic cancer. The purpose of this study is to identify the biological role of the Hh gene and to explore the potential target genes of Hh signal in pancreatic cancer.
Material and Methods: Two human pancreatic cancer cell lines, MiaPaCa-2 and Panc-1, were used. MiaPaCa-2 and Panc-1 were cultured and treated with Hh signal inhibitor, cyclopamine (5 μM, 10 μM, 20 μM, 40 μM) or tomatidine (5 μM), as a control. After 72 hours, the degree of apoptosis was measured by fluorescence activated cell sorting (FACS). Expressions of the Hh signal-related proteins were detected by Western blot analyses for Shh (sonic Hh) and Ptch (patched). To identify Hh signal-targeted genes, the oligo microarray containing a set of 22,746 human oligo was used. Expression and activity of cathepsin B, which was identified from our experimental results as one of the target genes of Hh signal, were examined by Western blotting and fluorometric assay, respectively.
Results: Cyclopamine treatment increased apoptosis dose-dependently in Panc-1 ($p < 0.05$) but not in MiaPaCa-2. Shh and Ptch levels were highly expressed in Panc-1 but not in MiaPaCa-2. However, Cyclopamine suppressed the expression of Ptch in Panc-1. After cyclopamine treatment in Panc-1, 138 genes were down-regulated by 2 folds or more and 24 genes by 3 folds or more. These down-regulated genes were cancer-related genes including Cathepsin B. Cyclopamine suppressed the expression and activity of cathepsin B in Panc-1.
Conclusions: Hh signal activation is associated with anti-apoptosis in some pancreatic cancer cells and this effect can be related with the activation of several target genes such as cancer-related genes including cathepsin B, which might be responsible for late mediator of pancreatic cancer.

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Tissue-specific transcription factors network in hepatocellular carcinoma progression

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The progression of epithelial tumors is closely associated with cell dedifferentiation. While the key role in the maintenance of hepatocyte