P – 136 Timed-flat infusion (TFI) 5-fluorouracil with irinotecan and oxaliplatin in pancreatic adenocarcinomas: A single institution experience with FIr/FOx regimen

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Introduction: Triplet chemotherapies, with fluoropyrimidines, platin derivatives and irinotecan, represent an option for first line treatment of metastatic/advanced pancreatic ductal adenocarcinoma (PDAC). FOLFIRINOX was often considered difficult to handle in common clinical practice, due to toxicity profile and features of PDAC patients, often frail with symptomatic disease. To increase tolerability and dose intensity (DI), we previously developed an alternative way of administration of 5Fluorouracil (5FU), with nocturnal "timed-flat infusion" (TFI) (from 10:00 PM to 10:00 AM), in several combination-schedules (breast, colorectal and gastric cancers). TFI mimics the chronomodulation of 5FU, without the dose-spike at 04.00 AM, 5FU bolus and folinic acid.

Methods: We report a retrospective analysis of 19 metastatic PDAC patients treated with FIr/FOx regimen, a schedule of weekly TFI/5FU for two nights at 900 mg/m2/night, associated to alternating irinotecan at 160 mg/m2 on days 1 and 15, and oxaliplatin at 80 mg/m2 on days 8 and 22, cycles repeated every 4 weeks.

Results: From February 2011 to February 2018, 19 patients were treated: 9 (47.4%) with standard FIr/FOx and 10 (52.6%) with modified regimens (defined as any projected dose reduction compared to standard) due to age, PS and comorbidities. Median age was 65 years (range 54-75), male/female ratio was 11/8. Ten patients (52.6%) had

ECOG-PS 0/1, 9 patients (47.4%) ECOG-PS 2. Fourteen patients (73.7%) had a primary/intermediate Cumulative Illness Rating Scale stage, 5 patients (26.3%) a Secondary one. Sixteen patients (84.2%) had un-resected primary tumor, 9 (47.4%) were located to the head and 10 (52.6%) to the body/tail. Two patients (10.5%) had obstructive jaundice at onset (carriers of biliary prosthesis). Thirteen patients (68.4%) had $\geq$ 2 involved organs. One patient had a metachronous disease previously treated with adjuvant gemcitabine and chemo-radiation therapy. Among 17 evaluable patients ORR was 35.2% (95%CI: 14.2-61.6) ad DCR was 58.8% (95% CI: 32.9-81.5). All patients were evaluable for efficacy: after a median follow-up of 42.6 months, median PFS and median OS were 4.4 months (95%CI: 2.3-11.8) and 11.8 months (95%CI: 2.3-19.9). Median Number of administered cycles was 3 (range: 1-11). The only G4 toxicity was mucositis in one patient (5.2%); G3 were: leuco/neutropenia (10.5%), asthenia (10.5%), diarrhea (5.2%), hypokaliemia (5.2%) and hypertransaminasemia (5.2%). No febrile neutropenia was observed; one patient died as result of adverse events. The median received DI were $\sim$ 80% of standard full dose for each drug: Irinotecan 60 mg/m2/week, oxaliplatin 34 mg/m2/week and 5FU 1380 mg/m2/week. Four patients (21.1%) were switched to a doublet regimen after the induction (6 months) due to toxicities. Two patients (10.5%) underwent ablative locoregional treatments of primary tumors after FIr/FOx. Nine out of 18 patients who progressed to FIr/FOx underwent a second line therapy (2 rechallenges with FIr/FOx, 6 gemcitabine-Abraxane, 1 gemcitabine).

Conclusion: Even if requires a careful management, FIr/FOx seems to be a feasible option for first line treatment of metastatic PDAC patients, particularly in needing of tumor shrinkage, with significant activity, high rDIs, and acceptable safety profile when compared to literature.