Background: Meloxicam and nimesulide have been studied as potential cancer immunomodulatory agents. Those drugs have been shown to have immune stimulatory effects on the tumor stroma and the microenvironment of several tumors including pancreatic ductal adenocarcinoma. They have several immune effects in vitro and in animal models. We compared the immunomodulatory activity of two preferential Cox-2 inhibitors drugs, meloxicam and nimesulide in advanced pancreatic cancer patient’s peripheral blood mononuclear cells (PBMCs) with good and poor Karnofsky.

Materials & Methods: Repository PBMCs from advanced pancreatic patients with Karnofsky < 50% (n=10) and > 80% (n=10) were stimulated with different concentrations of meloxicam and nimesulide in vitro. We performed dose-response curve with concentrations of both drugs ranging from 0.5, 1, 10, 50 and 100 µM and we performed the ELISPOT assays for Interferon-gamma using human anti-CD3 and CMV whole lysate as basal T cell stimulation. Th2 cytokines were measured as well by ELISPOT and Cytokine ELISA.

Results: In patients with Karnofsky > 80% both meloxicam and nimesulide were effective in promoting IFN-gamma production after stimulation with both drugs starting at 0.5 µM. The use of meloxicam was associated with significant production of IFN-gamma at 0.5 µM (p<0.001) and 1µM (p<0.0001). Nimesulide significantly induced IFN-gamma secretion at 0.5 µM (p=0.005), 1 µM (p=0.0002) and at 10 µM (p<0.0001).

Meloxicam and nimesulide treatment resulted in different responses in PBMCs IFG-gamma production from pancreatic cancer patients that had a Karnofsky <50%. Nimesulide was more effective than meloxicam at promoting IFN-gamma production at 1µM (p<0.005) and 10µM (p<0.0001). Meloxicam did not improve the IFN-gamma secretion at low doses such as 0.5, 1 and 10 µM (n.s.). However, meloxicam at 50 µM and 100 µM was able to induce IFN-gamma (p<0.05 and p<0.0001, respectively).

Additionally PBMCs treated with nimesulide in both groups were able to decrease Th2 cytokines such as IL-6, IL-18, TNF-alpha and IL-8 (statistical analysis in progress).

Discussion: This preliminary data suggests that the use of meloxicam and nimesulide as putative immunomodulatory drugs may be less effective when pancreatic patients have a
poor Karnosky although at high concentration they are effective. Also, the potent induction of IFN-gamma in patients with a good Karnofsky suggest synergy of these drugs in combination with standard of care treatment, immunogenic chemotherapy, anti-stroma strategies and active specific immunotherapy as a combinatorial approach to move forward into animal models of pancreatic cancer and eventually into the clinic.

Grant Support: Junior Physician Scientist Fellowship Grant from CICS.

**Category:** Immune Drug Development

**Keywords:** pancreatic cancer immunomodulation; anti-inflammatory drugs; IFN-gamma in pancreatic cancer patients