EUS guided local administration of large surface area microparticle paclitaxel with neoadjuvant chemotherapy in locally advanced pancreatic cancer: A single center experience

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Background and Aims

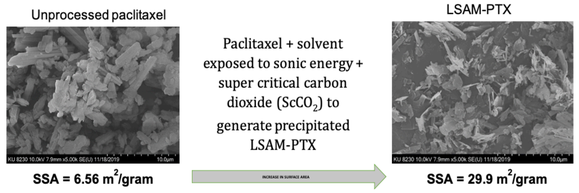
Locally advanced pancreatic cancer (LAPC) is defined as an unresectable tumor due to extensive vascular involvement without evidence of metastatic spread.

Neoadjuvant chemotherapy can downstage LAPC to resectable disease in about 10%–35% of patients resulting in an increased median survival.

Intravenous paclitaxel's hydrophobic, protein-bound nature, short half-life, and intermittent dosing combined with desmoplastic, fibrotic tumor microenvironment (TME) in LAPC hamper tumor tissue exposure time, resulting in suboptimal intratumoral (IT) bioavailability.

Large surface area microparticle paclitaxel (LSAM-PTX) was developed (NanOlogy, LLC) for IT delivery. LSAM-PTX has a mean particle size (Dv50) of ~2.5 µm and a 3-fold increase in specific surface area over unprocessed drug.

Large Surface Area Microparticle Paclitaxel (LSAM-PTX) Production Technology

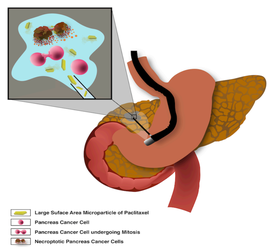


The relatively large particle size facilitates local drug retention, and increased surface area allows continuous drug release in tumor over an extended time, along with negligible systemic exposure.

We evaluated the histopathological and immunophenotypic profiling using multiplex immunofluorescence (mIF) on tumor site tissue from pre-LSAM-PTX biopsies and the resected tumor in patients with LAPC who were downstaged to resectable disease following EUS-guided local administration of LSAM-PTX in addition to standard systemic therapy.

Methodology

Data were collected prospectively on 6 of 13 (46%) LAPC subjects who received EUS-guided fine needle injection (EUS-FNI) of LSAM-PTX in addition to neoadjuvant chemotherapy and subsequently underwent surgery at our institution from 2018 to 2019 (NCT03077685).



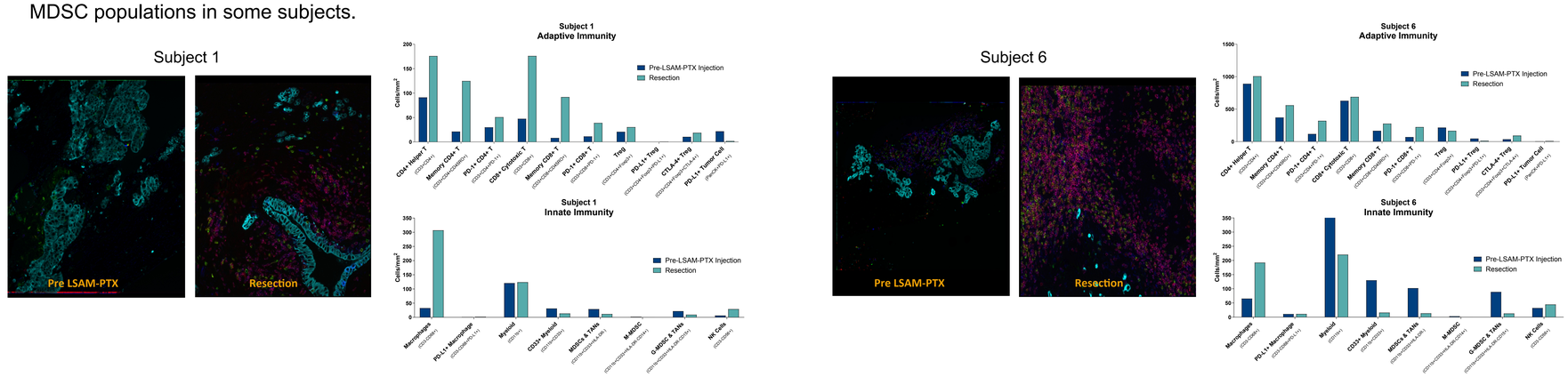
Each subject underwent two EUS-FNI procedures four weeks apart to deliver IT LSAM-PTX suspension (15 mg/mL) in a volume equivalent to 20% of the tumor volume up to 5 mL of drug.

Summary of Key Findings

- The mean duration from EUS-FNI to surgery was 6.91 months (range: 3.68-12.22 months).
- Five of six subjects (83%) had R0 resections. Of the five R0 resections, one subject had a pathologic complete response, one had 10% and two had 10-20% viable tumor, and one had a partial response with tumor regression.
- Focal necrosis reported in the lone subject with an R1 resection.

Subject Number	Treatment Effect	Notes
1	Complete response	No evidence of residual primary tumor; granulated to fibrous, markedly indurated mass
2	Excellent response	90% tumor appears to have responded to therapy; ill-defined indurated area (possibly a mass lesion) focal microcalcification, 3x1.5cm
3	Moderate response (grade 1)	Fibrosis and fat necrosis; heterogeneous, focally hemorrhagic ill-defined mass 4.2x4.2x4; minimal residual cancer
4	Moderate response	Fibrosis and necrosis consistent with chemo effect; Approximately 10-20% viable tumor; fibrosis and necrosis; focal hemorrhage and degeneration
5	Response grade 2	Ill-defined mass 3.5x3x1.5cm; residual tumor at 1.4cm in greatest dimension
6	Focal Necrosis	Focal necrosis; nodular lesion 5x4x3, grossly normal appearing pancreatic parenchyma extremely limited; peri-pancreatic tissues fibrotic and edematous

- Immunophenotypic profiling of tissue showed an increase in adaptive and innate immune cell density, an increase in NK cells in the TME, and decreases in the myeloid/ MDSC populations in some subjects.



Representative regions of interest (ROI) from mIF analysis of biopsy collected on Day 1 pre-LSAM-PTX injection and at resection demonstrate increases in density (cells/mm^2) of adaptive immune cells in the LAPC tumor microenvironment following LSAM-PTX treatment in two subjects. Light blue = PanCK+ tumor cells, yellow = CD4+ Helper T and magenta = CD8+ Cytotoxic T cells. Pre-LSAM PTX and resection ROIs were selected based on similar cell. 0.2X magnification. Changes in density of adaptive (top charts) and innate (bottom charts) immune cells in the TME are shown in bar graphs plotted as total number of each cell type divided by total area of all ROIs evaluated per slide.

Conclusions

- EUS-FNI of LSAM-PTX, added to neoadjuvant chemotherapy, was safe and resulted in a significant reduction in tumor volume, along with significant tumor necrosis, and favorable changes in tumor immunophenotypic configuration.
- These preliminary results suggest that adding LSAM-PTX to neoadjuvant chemotherapy could increase the rate of downstaging of LAPC to resectable disease and improve clinical outcomes.

References

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