C-29

Laser Capture Microdissection-Based Proteomics to Identify Immunotherapy Response Signatures in High-Grade Neuroendocrine Neoplasms

Patrick W. McGarrah, MD[1], Gunveen S. Sachdeva, MD[2], Kiran K. Mangalaparthi, PhD[2], Rondell P. Graham, MBBS[2], Mohamad Bassam Sonbol, MD[3], Jason S. Starr, DO[4], Thor R. Halfdanarson, MD[1], Rachel A. Eiring, PA-C[1], Timothy J. Hobday, MD[1], Akhilesh Pandey, MD, PhD[2]

[1]Mayo Clinic Department of Oncology, Rochester, MN; [2]Mayo Clinic Department of Laboratory Medicine and Pathology, Rochester, MN; [3]Mayo Clinic Division of Hematology/Oncology, Phoenix, AZ; [4]Mayo Clinic Division of Hematology/Oncology, Jacksonville, FL

BACKGROUND

Effective systemic therapy for high-grade neuroendocrine neoplasms (NEN G3) represents a critical unmet need. Immune checkpoint inhibitors (ICI) can produce uncommon, but sometimes very deep and durable responses. However, predictive biomarkers for response are lacking. We performed laser capture microdissection (LCM)-based deep proteomics to discover response-associated signatures.

METHODS

We analyzed archived tissues from 11 patients treated with ICI. H&E/IHC-reviewed 10-µm PEN sections were microdissected (~3,000 tumor cells/slide) and analyzed on a high-sensitivity timsTOF Ultra 2 mass spectrometer. Differential protein expression compared non-responders (NR) with responders (R) using 2-sample t-tests (fold change = NR/R). Overall survival from ICI start was calculated for each group.

RESULTS

Eleven LCM specimens from clinically annotated patients were analyzed (3 R, 8 NR specimens). Deep proteomic profiling was achieved across all specimens. Responders had longer ICI exposure and longer time from ICI start to death/last follow-up (p=0.0078) (Table). We identified 124 differentially expressed proteins (p<0.05; 78 lower and 46 higher in NR). NR tumors showed reduced oxidative stress/ferroptosis-associated proteins (MT1G, GSTP1, GSTO1) and reduced immune-associated proteins (HLA-DRB5,HLA-DPB1, PTPRC, LCP2). MMP15, an ECM-remodeling metalloproteinase, was detected in 7/8 NR and 0/3 R specimens.

CONCLUSIONS

LCM-based deep proteomics identified candidate ICI response signatures in NEN G3. Loss of oxidative stress/ferroptosis and immune-associated proteins in NR, together with NR-restricted MMP15, supports validation of these candidate predictive biomarkers. MT1G was

identified as the most promising novel biomarker. Next steps will test MT1G using a simple IHC assay and to validate the proteomic findings on a larger sample size.

Patient	Primary Tumor	IO Regimen	Best response	OS from ICI start (mo)	Status	MT1G (log2 intensity)
Responders						
1	G3 NET – pancreas	Pembrolizumab	PR	114.3	Alive	0.38
2	NEC – rectum	Ipi/nivo	CR	70.7	Alive	1.67
3	NEC – unknown primary	Ipi/nivo + OV	PR	13.1	Alive	2.65
Non-responders						
1	G3 NET – small bowel	Ipi/nivo	PD	16.4	Deceased	-2.74
2	NEC – rectum	Ipi/nivo + OV	PD	1.8	Deceased	-2.38
3	NEC – espohagus	Ipi/nivo	PD	5.4	Deceased	-1.11
4	NEC – unknown primary	Ipi/nivo	PD	6.3	Deceased	-2.16
5	NEC – tonsil	Ipi/nivo	PD	6.6	Deceased	-1.36
6	NEC – pancreas	Ipi/nivo + OV	PD	4.9	Deceased	-2.67
7	NEC – pancreas	Ipi/nivo	PD	10.0	Deceased	-1.42
8	NEC - rectum	Ipi/nivo	PD	3.7	Deceased	-2.87

ABSTRACT ID #36586