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Exploring Plasma-Derived Exosomes (PDEs) as a Response Biomarker in Neuroendocrine Tumors (NETs)

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BACKGROUND: Therapeutic advances have led to an improved prognosis of NETs, but the current response biomarkers (serum serotonin and chromogranin A) are unreliable. Our work (Hanif et al., Oncotarget 2020) showed that the expression of anti-apoptotic protein survivin in NETs is associated with a poor prognosis. Here, the role of survivin-expressing PDEs as a biomarker in gastroenteropancreatic (GEP) NETs is explored.

METHODS: Plasma (n=17) was obtained pre-and post-treatment with somatostatin analogues. Exosomes were isolated by size exclusion chromatography. Fractions containing <500ug/ml of protein were characterized by nanotracking analysis and phenotyped by imaging flow cytometry for exosome-markers (tetraspanins: CD9/CD63/CD81), NET-specific markers [chromogranin (CHR) neuron-specific enolase(NSE), synaptophysin(SYN)] and survivin(SUR). Associations between phenotypes and progression-free survival (PFS) and overall survival (OS) were evaluated using Cox regression models. Exosomes and serum biomarkers were correlated using Spearman correlation.

RESULTS: The median particle concentration and size were 1.6 X 10 11 /ml and 105 nm respectively. After a follow-up of 35 months, PFS was 32 months and OS was not reached. All the NET- specific markers and survivin were present on the tetraspanin+ particles.

The pretreatment presence of SUR+CHR+NSE+SYN- (HR 1.9,p=0.05), CHR+NSE+ (HR 1.9,p=0.05), CHR+ (HR 2,p=0.042) exosomes was associated with a worse PFS. Further, a reduction in these exosomes post-treatment was associated with a better PFS: SUR+CHR+NSE+SYN-(HR 0.4, p=0.025), CHR+NSE+ (HR 0.5 p=0.05), CHR+ (HR 0.6, p=0.086). There were no significant associations with OS likely due to only two deaths in the cohort. Serum serotonin and chromogranin did not have any significant associations with PFS or OS. Correlations were seen between post-treatment serum serotonin and SUR+NSE+CHR-SYN- (r=0.58,p=0.03), CHR+SUR-SYN-NSE-(r=0.58,p=0.03) and CHR+SYN+NSE+SUR- (r=0.5,p=0.04) exosomes.

CONCLUSION: PDEs in GEP-NETs express NET-specific markers and survivin. The prognostic value of exosome phenotypes SUR+CHR+NSE+SYN-, CHR+NSE+, and CHR+ warrants further investigation in a larger cohort.

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