C-2

Prognostic Significance of MEN1, ATRX, and DAXX Mutations in Pancreatic Neuroendocrine Tumors Treated with CAPTEM: Insights from a Multicenter Cohort

Ana De Jesus-Acosta[1], Jordan Kaplan[2], Chirayu Mohindroo[1], Hanfei Qi[3], Hao Wang[3], Jin He[4], Dan Laheru[1], Courtney Porfido[5], Nitya Raj[5], Diane-Reidy-Lagunes[5], Ka Wing Fu[6], Andrew Hendifar[6].

[1]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Medical Student, Johns Hopkins University School of Medicine; [3]Division of Quantitative Sciences, Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD; [4]Department of Surgical Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; [5]Memorial Sloan Kettering (MSK) Cancer Center, New York, NY, USA; [6]Cedars-Sinai Medical Center, Los Angeles, California, USA.

BACKGROUND

Capecitabine and temozolomide (CAPTEM) show promising response rates of 30–70% in pancreatic neuroendocrine tumors (pNETs). With multiple treatment options available, selecting the optimal sequence is challenging. Prognostic and predictive biomarkers are needed to identify patients who will benefit most. Mutations in ATRX, DAXX, and MEN1 are key drivers of pNETs, but few studies have examined how these combined molecular profiles affect response to CAPTEM.

METHODS

We conducted a multicenter retrospective study across Johns Hopkins Hospital (JHH), Memorial Sloan Kettering Cancer Center (MSK), and Cedars-Sinai Medical Center (CSM) to evaluate the role of ATRX, DAXX, and MEN1 mutations. Patients with histologically confirmed pNET who received CAPTEM and had molecular NGS data available were included. Clinical data collected comprised age, sex, race, MSI status, stage, surgery, metastatic status, systemic treatments, and survival. Statistical analyses included two sample t-test and chi-squared tests to examine associations between patient characteristics and mutations, and Kaplan-Meier methods and Cox regression models to evaluate survival outcomes.

RESULTS

The cohort included 275 patients from CSM (24.0%), JHH (30.2%), and MSK (45.8%), with a mean age at the initiation of CAPTEM of 57.3 years (SD 13.5) and 61.1% male. Most were White (71.6%) and presented with metastatic disease at diagnosis (72.4%) and CAPTEM start (89.8%). Prior surgery was reported in 34.9%, and CAPTEM was first-line treatment for 43.3%. MSI-High was found in 6.9% and MMR-proficient in 74.5% of patients; TMB was low in 63.3%, intermediate in 10.5%, and high in 4.7%. Mutation prevalence was 37.8% for MEN1, 18.5% for DAXX, 13.1% for ATRX, and 30.2% for combined DAXX/ATRX. CAPTEM discontinuation was mainly due to progression (42.9%) or therapy completion (41.1%). MEN1 mutations were associated with longer time to treatment failure (TTF; 25 vs. 9.8 months; HR 0.55, P<0.001) and longer overall survival (OS) (median OS 84.4 vs. 51.6 months; P=0.002) and remained independently associated with longer OS in multivariable analysis (HR [95% CI]: 0.52 [0.34, 0.80], P=0.003). Those with DAXX and/or ATRX mutations also showed longer OS (median OS 83.5

vs. 62.0 months; P=0.057), reaching statistical significance in multivariable analysis (HR [95% CI]: 0.64 [0.42, 0.99], P=0.043).

CONCLUSIONS

This is the largest analysis of CAPTEM treatment and molecular profiling in pNET patients. MEN1 mutations are independently associated with significantly longer TTF and OS, while DAXX/ATRX mutations are independently associated with OS. These findings suggest that profiling ATRX, DAXX, and MEN1 may help guide treatment decisions and optimize therapeutic sequencing in pNET. Further prospective studies are needed to validate these biomarkers for clinical use.

ABSTRACT ID 33482