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Leveraging Cell Mass Measurements To Assess Drug Efficacy For Gastroenteropancreatic Neuroendocrine Tumor Liver Metastases And Advanced Adrenocortical Carcinoma

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BACKGROUND

Although surgical debulking is an accepted therapeutic strategy for selected patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) or adrenocortical carcinoma (ACC), recurrence is the rule rather than the exception. Current preclinical models struggle with translational applicability and access to tissue at time of surgery has limited high-throughput utility for new drug discovery. To address this unmet need, we investigated single tumor cell mass measurements curated with inline machine-learning based image classification using tissue from the operating room to identify candidate drugs for a personalized medicine approach.

METHODS

Tumor biopsies from metastatic small bowel neuroendocrine tumors (SBNET) and pancreatic neuroendocrine tumors (PNET) liver metastases and advanced ACC tumors were collected intraoperatively. Tumor cells were isolated from tumor biopsies and assessed for viability utilizing CellTiter-Glo and flow cytometry. Cells were treated with FDA-approved drugs including everolimus, etoposide, doxorubicin, and cisplatin. Drug response was measured post-treatment upon passing single cell suspensions through a suspended microchannel resonator (SMR) to assess cell mass. Brightfield images were captured as cells passed through the SMR and annotated using machine-learning based classification to identify intact cells from debris particles for assessment of drug response. Drug response was assigned a value between 0 and 100, with >50 indicating a significant response to the treatment. Patient clinical response to therapy was defined by RECIST criteria.

RESULTS

Tumor biopsies were collected from 13 SBNET patients with median cell purity 76% (95% CI 70-92%) and median viability 92% (95% CI 90-95%), 6 PNET patients with median cell purity 70% (95% CI 50-88%) and median viability 92% (95% CI 60-97%), and 9 ACC patients with median cell purity 65% (95% CI 10-80%) and median viability 96% (95% CI 90-99%). Drug treatments were successfully performed in 69% SBNET samples, 66% PNET samples, and 66% ACC samples. For GEP-NETs, 63% SBNET and 100% PNET samples demonstrated significant drug response to everolimus. For ACC, treatment with etoposide, doxorubicin, and cisplatin demonstrated significant drug response in 40%, 33%, and 40% of samples, respectively. This lack of response to etoposide, doxorubicin, and cisplatin aligned with these patients' clinical disease progression despite previous treatment with these drugs.

CONCLUSIONS

This study indicates drug efficacy may be assessed using single-cell mass measurements of tumor cells. This methodology carries implications for selecting personalized therapies to optimize treatment plans for patients with metastatic neuroendocrine tumors and adrenocortical carcinoma.

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