PRE-SELECTION OF PATIENTS WHO WOULD RESPOND TO COMBINATION OF CHEMOTHERAPY AND LOW DOSE IMMUNOTHERAPY USING HUMAN HISTOCULTURE PLATFORM

Background Only 1–3 % of patients with Head and Neck Squamous Cell Carcinoma (HNSCC) in low- and middle-income countries can afford Nivolumab treatment even though it is approved for recurrent and metastatic disease.\(^1\) Low Dose Nivolumab (LDN) has shown similar efficacy compared to Standard Dose Nivolumab (SDN) in renal and lung cancer.\(^2\)\(^3\) A recent study demonstrated that HNSCC patient sub-cohort treated with chemotherapy (CT) and LDN showed improved progression-free and overall survival compared to sub-cohort treated with CT alone.\(^1\) To better understand the added benefit of the combination treatment, it is important to rule out the contribution of CT alone in the responding patients that might not result in a durable response. To address this, we employed the Farcast\textsuperscript{TM} TruTumor, a near native human histo-culture platform which can compare multiple treatment response simultaneously for the same patient sample.

Methods Fresh surgically resected HNSCC samples (n=20) along with matched blood were collected from consenting patients. Thin explants were generated and distributed into arms. These arms were treated in culture with either LDN (7.3 \(\mu\)g/ml) or SDN (132 \(\mu\)g/ml)+erlotinib (2.5 \(\mu\)g/ml)+Carboplatin (37.1 \(\mu\)g/ml) or CT (Methotrexate (220.8 \(\mu\)g/ml)+erlotinib (2.5 \(\mu\)g/ml)+celocobib (0.7 \(\mu\)g/ml) or Paclitaxel (2.7 \(\mu\)g/ml)+Carboplatin (37.1 \(\mu\)g/ml) alone or CT+LDN for 72 hours. The response was evaluated using histo-cytometry.

Results Both SDN and LDN-treatment led to effective masking of Programmed cell death protein 1 (PD1) expression. No significant difference was observed in tumor cytotoxicity response between LDN and SDN in the same samples (n=8). Analysis of immune cell types and activation markers such as CD8+Granzyme-B+; CD8+Ki67+ T cells also showed no significant difference between LDN and SDN treatments.Comparable IFN-\(\gamma\) cytotoxicity and cytotoxicity release were compared.

We next compared response to CT alone or CT+LDN in the same sample (n=12). Ten out of 12 samples did not show a significant difference in tumor content on treatment with CT+LDN compared to CT alone. Five out of these 10 samples showed a significant increase in cleaved caspase expression in tumor, primarily driven by CT treatment. In two samples CT+LDN showed significant drop in tumor content but not in CT or SDN alone, clearly implicating the benefit of combination treatment.

Conclusions The Farcast\textsuperscript{TM} TruTumor platform thus provides the unique opportunity to identify patients who would truly benefit from treatment with LDN+CT combination. An observational trial is underway to correlate the response observed in our platform with response of the patient in the clinic.

REFERENCES

Ethics Approval The Institutional Ethics Committee (IEC) from the sample collection centers approved the protocol (protocol # FCB-PROTOCOL-01) and informed consent for participation in the approved study was obtained from every donor.

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