

Poster 14 Hsp90 α/β strong expression stratifies primary colorectal cancer patients (UICC IIb-IV) for short survival and response to targeted therapy

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Background

Benefit in targeted therapy is limited in metastatic colorectal cancer (CRC). A promising new candidate for targeted therapy are cytosolic, heat shock protein 90 α and heat shock protein 90 β (Hsp90 α/β). This study tested the prognostic and predictive impact of Hsp90 α/β protein expression in 89 primary (p) CRC patients.

Material and methods

Eighty-nine samples of pCRC were immunohistochemically stained and the results were correlated with 10-year survival data. The effectiveness of Hsp90 inhibitors e.g., ganetespib (Gan) and pimitespib (Pim) was analyzed in CRC cell lines (HCT-116; HT-29 and Caco-2) and the Patient Derived Colorectal Cancer Spheroid (PDCS) model. Additionally, the combination of Hsp90 inhibitors with standard chemotherapeutics e.g. 5-FU (F), 5-FU+Oxaliplatin (FO), 5-FU+Irinotecan (FI), encorafenib and Trastuzumab were tested.

Results

Hsp90 α/β overexpression (>40% positive cancer cells) was found in 27% of patients and predicted early recurrence (<16 months, $p=0.047$), poor progression-free survival (HR 3.250, $p=0.007$) and overall survival (HR 3.029, $p=0.022$). Hsp90 α/β overexpression, when combined with BRAF-V600E mutation or Her2/neu Score >3, was linked to a worse prognosis (all $p<0.05$).

Hsp90 inhibitors Gan and Pim as single agents showed direct anti-tumor effects in CRC cell lines HCT-116, HT-29, and Caco-2 but were less effective than traditional chemotherapies. Combining Gan or Pim with encorafenib or trastuzumab improved efficacy compared to monotherapies in HT-29 and Caco-2 cells (all $p<0.05$).

Gan and Pim also had a chemosensitizing effect, enhancing the efficacy of 5-FU, FO or FI in HCT-116, HT-29, and Caco-2 cells (all $p<0.05$). F+Gan or F+Pim combinations outperformed standard chemotherapies.

In patient-derived spheroids, Hsp90 α/β expression correlated with response to Hsp90 inhibitors. In those individual spheroid models the superiority of F+Gan and F+Pim to F, FI, Gan, Pim and most interesting to FO could be confirmed.

Conclusion

Hsp90 α/β overexpression represents a prognostic and predictive biomarker for locally advanced and metastatic CRC and could potentially replace Oxaliplatin in chemotherapy regimens.