Targeted treatments in gastric adenocarcinoma circulating tumour cells: Is combination therapy the answer?

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Background & objectives

Metastatic gastric adenocarcinomas (mGAC), one of the deadliest cancers worldwide, often harbour gene alterations in receptor tyrosine kinases (RTKs) and their downstream effectors. These include the mesenchymal epithelial transition factor (c-Met) encoded by the *MET* proto-oncogene, the epidermal growth factor receptor (EGFR) encoded by *EGFR,* and genes encoding proteins in the phosphatidylinositol 3-kinases (PI3K)/mammalian target of rapamycin (mTOR) signalling pathway. In particular *PIK3CA,* encoding the p110α protein, a subunit of PI3K, is recurrently mutated in mGACs. Dysregulation of these signalling pathways represents one of the main causes of chemoresistance in mGAC and combinatorial targeted treatments may overcome potential compensatory mechanisms that arise.

In this study we use our unique human mGAC-derived circulating tumour cell line, UWG02CTC, which harbours activating *MET* and *PIK3CA* alterations and *EGFR* amplification, to investigate targeted single and combination drug responses against these key mutations, and explore functional consequences under different culture conditions.

Methods

We used Western blot analysis and MTS assays to determine the effects of different drug treatments in 2-dimenstional and 3-dimensional tissue culture models, and organotypic invasion model.

Results

In monotherapy, only PI3K inhibition demonstrated significant cytotoxicity. Despite *MET* mutations, c-Met inhibition with AMG-337 or capmatinib had no cytotoxic effect on either cell line as 2-dimensional or spheroid cultures. The PI3K p100α-subunit inhibitor PIK-75 was highly cytotoxic towards UWG02CTC cultured under 2- or 3-dimensional conditions (IC_{50} range 42.6 to 10.7 nM, respectively). Only a limited effect was seen with the EGFR inhibitor gefinitib, however, combination treatment with PIK-75 and gefitinib was synergistic. This effect was most pronounced in 3D models, and overcame the resistant populations seen in standard culture or embedded in matrix conditions. C-Met inhibition was not synergistic in combination with any other drugs.

Conclusion

In summary, our results demonstrate dual targeting of PI3K and EGFR in a mGAC CTC cell line was promising and may offer a novel treatment approach in mGAC harbouring alterations in these pathways. We also show key sensitivity differences depending on the growth conditions, suggesting targeting CTCs may improve efficacy.