Methodology Patients (n=49) undergoing maximal-effort upfront-debulking surgery for advanced HGSOC had a tumour mapping of their tumour dissemination. Tumour biopsies were collected (range 4–15) from patients, and also at time of relapse (n=10 patients). DNA was extracted from tumours (5 per patient, n=49 patients plus paired relapse samples) and Illumina Human OmniExpress genotyping performed. Allele-specific recombination (HR) scores were estimated using a scarHRD algorithm, applying a cut-off >42 for HR-deficient.

Results Extensive genomic variations in CN signature exposures for different patients’ tumours were observed, including between matched primary and relapse tumours. Increased CN signature exposure scores for Signatures 2 (p=0.00017), 4 (p=0.0029) and 6 (p=0.001) correlated with poor outcome in platinum-resistant/refractory patients, increased Signature 3 correlated with favourable outcome (p=0.00018) for platinum-sensitive and no-relapse patients. Variations in HR scores were observed across the cohort with one fifth of patients presenting with a mixed HR score profile across their tumour deposits, demonstrating both HR-deficient and HR-proficient tumours within patients.

Conclusion Extensive CN variations in CN signature scores and mixed HR-deficiency/proficiency scores indicates that a single tumour biopsy does not accurately depict disseminated HGSOC biology, and therefore should not be used as the basis to derive biomarker profiles for prediction of patient treatment responses or outcomes.
Conclusion Low ALI was associated with higher perioperative complications and poorer survival in ovarian cancer. The utility of preoperative ALI as a prognostic marker in ovarian cancer should be assessed in prospective studies.

Conclusion Upon MTX-R, choriocarcinoma cells favor redirection of serine to GSH production and this may help with combating chemotherapy-induced reactive oxygen species (ROS) accumulation and hence participate in the resistant phenotype. Concomitant de novo serine synthesis inhibition and targeting upstream pathways or molecules that block the synthesis of glutathione (GSH), as indicated by the increased levels of this metabolite in resistant cells.

Trophoblastic diseases

2022-RA-701-ESGO ELUCIDATING MECHANISMS UNDERLYING METHOTREXATE RESISTANCE VIA QUANTITATIVE PROTEOMICS ANALYSIS OF GTN PATIENT SAMPLES AND CHORIOCARCINOMA CELL LINES: A CRUCIAL ROLE FOR SERINE METABOLISM

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Introduction/Background Choriocarcinoma is an aggressive type of Gestational Trophoblastic Neoplasia (GTN). Patients with low-risk GTN following a molar pregnancy frequently commence therapy with single-agent methotrexate (MTX). Unfortunately, many develop resistance (MTX-R) and require either another single agent or more toxic combination agent chemotherapy to achieve remission. Understanding the molecular mechanisms of MTX-R may identify interventions to prevent or reverse this.

Methodology We employed proteomics profiling to identify changes that accompany MTX-R in post molar GTN patient samples and in choriocarcinoma cell lines that were either MTX sensitive (MTX-S) or resistant (MTX-R).

Results Quantitative mass spectrometry (MS) analysis revealed that the de novo serine synthesis pathway was one of the most downregulated pathways both in the MTX-R patients and in the resistant choriocarcinoma cell line. Decreased glucose-derived serine synthesis is supported by our findings that choriocarcinoma MTX-R cells have a less active glycolytic pathway. Concomitant de novo serine synthesis inhibition and serine deprivation from the growth medium promoted MTX-R in cell lines. Moreover, examination of the expression levels of 1-Carbon metabolism enzymes suggested a different utilization of serine, the major 1-Carbon donor, between sensitive and resistant cells. In particular, MTX-R cells may be channeling serine into pathways crucial for cell survival, such as the synthesis of glutathione (GSH), as indicated by the increased levels of this metabolite in resistant cells.

Conclusion Upon MTX-R, choriocarcinoma cells favor redirection of serine to GSH production and this may help with combating chemotherapy-induced reactive oxygen species (ROS) accumulation and hence participate in the resistant phenotype. In contrast, MTX-sensitive cells utilize serine for nucleotide synthesis and the maintenance of proliferation. Hence, targeting upstream pathways or molecules that block the synthesis of serine in combination with or without MTX treatment could improve therapeutic response in patients with MTX resistance.