REPURPOSING MEDROXYPROGESTERONE ACETATE AND MEFENAMIC ACID FOR PLATINUM-RESISTANT OVARIAN CANCER

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High-grade serous ovarian carcinoma (HGSOC) is the most prevalent and lethal subtype of ovarian cancer, frequently characterized by resistance to platinum-based chemotherapy. Members of the aldo-keto reductase subfamily 1C (AKR1C) have been associated with both chemoresistance and hormone-regulated tumor progression, though their exact contribution to HGSOC remains to be fully elucidated. To investigate this, we analyzed transcriptomic profiles from The Cancer Genome Atlas (TCGA) to assess expression patterns of *AKR1C1–3* and *NFE2L2* (encodes NRF2, a key oxidative stress regulator) in HGSOC tumors. Notably, platinum-resistant samples exhibited stronger co-expression relationships among *AKR1C* genes. Kaplan–Meier Plotter analysis revealed that elevated expression of *AKR1C1, AKR1C2*, and reduced expression of *NFE2L2* was associated with reduced survival in patients with serous ovarian cancer. qPCR and RNAseq analysis confirmed higher expression of A*KR1C1–3* in the least carboplatin-sensitive cell lines (Caov-3 and COV362), although *NFE2L2* expression patterns did not consistently reflect those seen in clinical survival data. We next evaluated the antitumor activity of two FDA-approved AKR1C inhibitors, medroxyprogesterone acetate and mefenamic acid. Both agents significantly decreased cell viability and impaired migratory capacity, whether administered alone or in combination with estrone sulfate and/or carboplatin. In several assays, their efficacy matched or exceeded that of carboplatin. Importantly, medroxyprogesterone acetate and mefenamic acid induced apoptosis without triggering necrosis in either cell line. In contrast, carboplatin failed to activate apoptotic pathways and caused delayed necrosis only in Caov-3 cells after 72 hours, suggesting a slow, non-apoptotic mechanism of cell death. Together, these results highlight *AKR1C* and *NFE2L2* as candidate prognostic markers in HGSOC and suggest that repurposing medroxyprogesterone acetate and mefenamic acid may offer a promising therapeutic strategy against platinum-resistant tumors.

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