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Oral Communication 1

Ivermectin: an ally to reverse P-glycoprotein-associated multidrug resistance in ovarian cancer

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Abstract

Background: The standard treatment for ovarian cancer (OC) involves carboplatin and paclitaxel, which can be followed by PARP inhibitors (PARPi) [1]; however, resistance to therapy is common. Increased drug efflux is a well-described mechanism of resistance to paclitaxel and PARPi [2]. Prior treatment with paclitaxel may increase P-gp upregulation and indirectly induce PARPi resistance [3]. Ivermectin, a broad-spectrum antiparasitic agent, has been found to enhance the anti-cancer efficacy of chemotherapeutic drugs and, in some cases, reverse resistance [4]. Ivermectin can act as a chemosensitizer by blocking drug efflux capacity, increasing intracellular drug accumulation, and enhancing antineoplastic efficacy [5]. **Objectives:** We aim to study the therapeutic benefits of combining paclitaxel or olaparib with ivermectin. **Methods:** To achieve this, we measured the cytotoxic effects of paclitaxel and olaparib separately and also in combination with ivermectin on two tumor chemoresistant (OVCAR8 and OVCAR8 PTX R) and one non-tumoral (HOSE6.3) cell lines. To measure cellular viability, we used the Presto Blue assay. We also assessed the synergistic interactions using the SynergyFinder Plus Software. **Results:** Our findings show that OVCAR8 PTX R, a paclitaxel-resistant cell line established in our laboratory, is also resistant to olaparib. We also discovered that ivermectin can increase the sensitivity of tumor cells to antineoplastic drugs and enhance their effectiveness. When paclitaxel and olaparib were combined with ivermectin, it resulted in the highest cytotoxic effect and the strongest synergistic effect compared to drugs alone. **Conclusions:** It would be advisable to assess P-gp expression before administering PARPi to patients who failed paclitaxel therapy. Both drugs are P-gp substrates, and their active efflux from cells can compromise clinical response. The potential of combining ivermectin with paclitaxel or olaparib is promising. Our results show that ivermectin, a substrate and modulator of P-gp, has the potential to reverse chemoresistance mediated by P-gp blockage.

Keywords: chemoresistance; paclitaxel; P-glycoprotein; olaparib; ovarian cancer

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