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Malignant Ovarian Cancer Ascites Confers Platinum Chemoresistance to Ovarian Cancer Cells: A Combination Treatment with Crizotinib and 2 Hydroxyestradiol Restore Platinum Sensitivity

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Abstract : Ovarian cancer (OC), the second most common form of gynecological malignancy, has a poor prognosis and is frequently identified in its late stages. The recommended treatment for OC typically includes a platinum-based chemotherapy, like carboplatin. Nonetheless, OC treatment has proven challenging due to toxicity and development of acquired resistance to therapy. Chemoresistance is a significant obstacle to a long-lasting response in OC patients, believed to arise from alterations within the cancer cells as well as within the tumor microenvironments (TME). Malignant ascites is a presenting feature in more than one-third of OC patients. It serves as a reservoir for a complex mixture of soluble factors, metabolites, and cellular components, providing a pro-inflammatory and tumor-promoting microenvironment for the OC cells. Malignant ascites is also associated with metastasis and chemoresistance. In an attempt to elucidate the role of TME in chemoresistance of OC, we monitored the ability of soluble factors derived from ascites fluids to affect platinum sensitivity of OC cells. This research, compared ascites fluids from non-malignant cirrhotic patients to those from OC patients in terms of their ability to alter the platinum sensitivity of OC cells. Our findings indicated that exposure to OC ascites induces platinum chemoresistance on OC cells in 11 out of 13 cases (85%). In contrast, 75% of cirrhosis ascites (3 out of 4) failed to confer platinum chemoresistance to OC cells. Cytokine array analysis revealed that IL-6, and to a lesser extent HGF were enriched in OC ascites, whereas IL-22 was enriched in cirrhosis ascites. Pharmaceutical inhibitors that target the IL-6/JAK signaling pathway were mildly effective in overcoming the platinum chemoresistance induced by malignant ascites. In contrast, Crizotinib an HGF/c-MET inhibitor, and 2-hydroxyestradiol (2HE2) were effective in restoring platinum chemoresistance to OC. Our findings demonstrate the importance of OC ascites in supporting platinum chemoresistance as well as the potential of a combination therapy with Crizotinib and the estradiol metabolite 2HE2 to regain OC cells chemosensitivity.

Keywords : ovarian cancer, platinum chemoresistance, malignant ascites, tumor microenvironment, IL-6, 2-hydroxyestradiol, HGF, crizotinib
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