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Low-dose naltrexone suppresses ovarian cancer and exhibits enhanced inhibition in combination with cisplatin

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Abstract

Ovarian cancer is the leading cause of death from gynecological malignancies. Although initial therapeutic modalities are successful, 65% of these women relapse with only palliative treatments available thereafter. Endogenous opioids repress the proliferation of human ovarian cancer cells *in vitro*, and do so in a receptor-mediated manner. The present study examined whether modulation of opioid systems by the opioid antagonist naltrexone (NTX), alone or in combination with standard of care therapies (taxol/paclitaxel, cisplatin), alters human ovarian cancer cell proliferation in tissue culture and tumor progression in mice. Administration of NTX for six hours every two days, but not continuously, reduced DNA synthesis and cell replication from vehicle -treated controls in tissue culture. Moreover, brief exposure to NTX in combination with taxol or cisplatin had an enhanced anticancer action. Mice with established ovarian tumors and treated with a low dosage of NTX (LDN), which invokes a short period of opioid receptor blockade, repressed tumor progression in a non-toxic fashion by reducing DNA synthesis and angiogenesis but not altering cell survival. The combination of LDN with cisplatin, but not taxol, resulted in an additive inhibitory effect on tumorigenesis with enhanced depression of DNA synthesis and angiogenesis. LDN combined with cisplatin alleviated the toxicity (e.g. weight loss) associated with cisplatin. LDN treatment upregulated the expression of the opioid growth factor (OGF, chemical term ([Met^5]-enkephalin) and its receptor, OGFr. Previous tissue culture studies have reported that OGF is the only opioid peptide with antiproliferative activity on ovarian cancer cells, with OGF action mediated by OGFr. Thus, the common denominator of intermittent opioid receptor blockade by short-term NTX or LDN on ovarian cancer proliferation and tumorigenesis recorded herein appears to be related to the OGF–OGFr axis. These preclinical data may offer a non-toxic and efficacious pathway-related treatment that can benefit patients with ovarian cancer.

Keywords

cell proliferation | low-dose naltrexone | ovarian cancer | opioid antagonist | opioid growth factor (OGF) | opioic