Low dose naltrexone (LDN): Harnessing the body's own chemistry to treat human ovarian cancer

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Researchers at The Pennsylvania State University College of Medicine, Hershey, Pennsylvania have discovered that a low dose of the opioid antagonist naltrexone (LDN) has an extraordinarily potent antitumor effect on human ovarian cancer in tissue culture and xenografts established in nude mice. When LDN is combined with chemotherapy, there is an additive inhibitory action on tumorigenesis. This discovery, reported in the July 2011 issue of *Experimental Biology and Medicine,* provides new insights into the pathogenesis and treatment of ovarian neoplasia, the 4th leading cause of cancer-related mortality among women in the United States.

The strategy of LDN therapy in repressing cancer was first reported over 30 years ago by Drs. Zagon and McLaughlin (Science 221:671-673). Naltrexone (NTX) is a general opioid receptor antagonist devoid of intrinsic activity that results in a compensatory elevation in endogenous opioids and opioid receptors. Blockade of opioid peptides from opioid receptors for a short time each day (4 to 6 hr) with LDN provides a sufficient window of time (18-20 hr) for the elevated levels of endogenous opioids and opioid receptors to interact and elicit a response: inhibition of cell proliferation. Thus, LDN acts as a decoy to upregulate native opioids and opioid receptors. When NTX is metabolized and no longer present, an enhanced opioid-receptor effect is permitted to occur. The endogenous opioid peptide, opioid growth factor (OGF) (chemical term = [Met5]-enkephalin) and its receptor (OGFr) is related to LDN

action, and constitutes a tonically active inhibitory axis that suppresses cell proliferation through a depression in DNA synthesis by way of cyclin-dependent kinase inhibitory pathways. In the case of human ovarian cancer, this laboratory (Amer. J. Physiol. 296:R1716-1725, 2009) previously found that the OGF-OGFr axis is present and functional in human ovarian cancer.

The present study addressed the question of whether modulation of the OGF-OGFr axis by LDN could alter the progression of established ovarian tumors. Moreover, the authors asked whether LDN can be combined with standard chemotherapy to invoke an even greater effect on ovarian cancer. A model of LDN in tissue culture was established that exposed human ovarian cancer cells to NTX for 6 hr every two days, resulting in reduced DNA synthesis and cell replication from vehicle subjected controls. When a short term exposure to NTX was combined with standard of care chemotherapeutic agents, taxol or cisplatin, an enhanced anticancer action relative to either drug was observed. The effects of LDN, but not taxol or cisplatin, could be reversed, indicating the non-toxic nature of LDN. Although favorable results with LDN alone and in combination with chemotherapeutic drugs were recorded in a tissue culture setting, this begged the question of whether LDN was effective on tumors transplanted into mice. Using nude mice with established xenografts of human ovarian cancer, LDN was found to repress tumor progression, reducing DNA synthesis and angiogenesis but not altering cell survival. LDN's repression of cancer progression was comparable to that of cisplatin or taxol. However, the combination of LDN with cisplatin, but not taxol, had an even greater antitumor effect than LDN or taxol alone. Moreover, cisplatin was toxic to the mice, as detected by weight loss. However, LDN in combination with cisplatin attenuated the toxicity of this chemotherapeutic agent, indicating that LDN was protective of the adverse events elicited by a chemotherapeutic drug. Finally, LDN was discovered to upregulate the expression of both OGF and OGFr, indicating that this endogenous

opioid system, which inhibits cell proliferation, was activated by LDN.

The research team was comprised of Dr. Ian S. Zagon, Distinguished University Professor, and Dr. Patricia J. McLaughlin, Professor, along with a doctoral student, Dr. Renee N. Donahue, in the Department of Neural & Behavioral Sciences. Drs. Zagon and McLaughlin have extensive collaborations focused on demonstrating the remarkable properties of LDN and OGF in a variety of preclinical and clinical studies. LDN has proven successful in Phase I and II clinical trials in the treatment of Crohn's disease, and OGF has been found to be safe and efficacious for pancreatic cancer. Co-author Dr. McLaughlin states: "Given the extraordinary biological control of the OGF-OGFr axis with respect to cell proliferation, and the unique modulatory capability of LDN to enhance opioid-receptor response by way of native biological processes, this is particularly attractive as a biological-based treatment in arresting the progression of ovarian cancer." Dr. Zagon adds that "More than 75% of women are diagnosed with ovarian cancer in advanced stages because of a lack of diagnostic biomarkers. Although the initial clinical response to cytoreductive surgery and adjuvant chemotherapy is excellent, nearly 65% of advanced-staged patients relapse within 2 years. All subsequent treatments are pallative. Thus, the clinical implications of our study speak to the urgency for initiating clinical trials using LDN in the treatment of advanced ovarian cancer."

Steven Goodman, Ph.D. Editor-in-Chief of Experimental Biology and Medicine said "Researchers at The Pennsylvania State University College of Medicine have discovered that a low dose of the opioid antagonist naltrexone markedly suppresses progression of human ovarian cancer transplanted into mice. Low dose naltrexone combined with cisplatin, but not taxol, had an additive inhibitory action on tumorigenesis. Therefore low dose naltrexone offers a non-toxic and efficacious biologic pathway-related treatment that may benefit patients with this ovarian cancer."