Annals of
Reviews and Research

Juniper Publishers
key to the Researchers

Review Article
Volume 4 Issue 2 - October 2018

Ann Rev Resear

Low-Dose Naltrexone in Combination with High-Dose Vitamin C in Cancer Patients: Our Experience and Medical Literature Review - it should be Reinforced in Our Practices of Integrative Oncology

Raúl H Morales-Borges*and NelmarieÁlvarez-Rodríguez

Integrative Optimal Health of Puerto Rico, USA

Submission: September 10, 2018; **Published:** October 25, 2018

***Corresponding author:** Raúl H Morales-Borges, New Alliance Integrative Research, LLC29Washington Street Suite #107Juan, USA, PR 00907-1509, Tel:(78)722-0412; Fax:(787)723-0554; Email: raul.morales.borges@gmail.com/raul@nairesearch.org

Keywords: Low-dose naltrexone; High-dose vitamin C; Cancer; Integrative oncology

Abbreviations: NTX: Naltrexone; LDN: Low-Dose Naltrexone; HDIVC: High-dose intravenous Vitamin C; ROS: Reactive Oxygen Species; NER: Nucleotide Excision Repair; HIF: Hypoxia-Inducible Factor; SCLC: Small Cell Lung Cancer; ALA: Alpha-Lipoic Acid

Introduction

Naltrexone (NTX) is a long-acting oral pure non-selective antagonist of opioid receptors approved for the treatment and rehabilitation therapy in alcohol addiction and discharged opiate addicts to eliminate dependence and to maintain a normal life and prevent or reduce relapse [1,2]. The usual dose of 50 mg one tablet oral per day. The mechanism of action is a complete opioid blockade, which removes the pleasure sensation created by endorphins. In recent years, there have been some novel and significant findings on the off-label usage of NTX. Within a specific dosage window, Low-Dose Naltrexone (LDN) can act as an immunomodulator in multiple autoimmune diseases and malignant tumors as well as alleviate the symptoms of some mental disorder [2,3]. LDN in the range of 3-4.5 mg per day has been shown to have the opposite effect – brief opioid receptor blockade with resulting upregulation of endogenous opiate production. Through the work of Bihari and Zagon, it has been determined that the level of endogenous opiate methionine-enkephalim is Increased by LDN [1]. Met-enkephalin is involved in regulating cell proliferation and can inhibit cancer cell growth in multiple cell lines. LDN increases the levels of met-enkephalin, and this has a potential to inhibit cancer growth in humans.

Meanwhile, High-dose intravenous Vitamin C (HDIVC)) has been studied and applied in patients with cancer [4-7]. There is an excellent book by Gonzalez & Miranda-Massari[4] that reviewed the use and role of high dose vitamin C in cancer patients. Vitamin C breaks down to generate hydrogen peroxide, which can damage tissue and DNA. It has been demonstrated that DNA is susceptible to damage by Reactive Oxygen Species (ROS). 8-oxo-2'-deoxyguanosine (8-oxodG) is probably one of the most abundant DNA lesion formed during oxidative stress and this potentially mutagenic lesion causes G --> T transversions and is therefore an important candidate lesion for repair, particularly in mammalian cells. Several pathways exist for the removal, or repair, of this lesion from mammalian DNA. One alternative pathway in humans is the Nucleotide Excision Repair (NER), which could possibly remove the 8-oxodG lesion. Lunec Jet al.[5] proposed that redox-active components of the diet, such as vitamin C, may promote such repair, affecting NER specifically.

Another important mechanism is the enhanced enzymatic degradation of Hypoxia Indecible Factor (HIF) 1 alpha by ascorbic acid. Hypoxia-Inducible Factor (HIF) plays a vital role in determining patterns of gene expression in cancer [6]. HIF is down-regulated in oxygenated cells by a series of Fe (II) and 2-oxoglutarate dependent dioxygenases that hydroxylate specific residues in the regulatory HIF-alpha subunits. Because these enzymes require ascorbate for activity in vitro we analyzed the effects of ascorbate on HIF in human cancer cell lines. Ascorbate at physiological concentrations (25 micro M) strikingly suppressed HIF-1alpha protein levels and HIF transcriptional targets, particularly when the system was oncogenically activated in normoxic cells. Similar results were obtained with iron supplementation. These results indicate that both ascorbate and iron availability have significant effects on HIF and imply that the system is commonly regulated by limiting hydroxylase activity under normoxic tissue culture conditions.

In this review, we are presenting our experience with few cases of cancer treated with LDN plus/minus HDIVC as active treatment as well as others with chemotherapy and hormone therapy with that combination. A review of medical literature was done, and this is the second time where this combination got published as an effective therapy for cancer patients.

Basics of LDN in Cancer

Opioids are implicated in the regulation of tumor growth and biology [8-11]. Maneckjee& Minna [12] found that methadone has significant growth inhibitory effect on lung cancer cells in Nitro and in vivo. They used Small Cell Lung Cancer (SCLC) and non-SCLC cell lines. They performed growth assays such as the colorimetric MTT assay, receptor binding assays and intracellular cAMP measurements. Only brief exposure to methadone was required for loss of cell viability and this is referred by cycloheximide and Actinomycin D. NTX blocks methadone growth inhibition. Methadone causes a decrease in intracellular cAMP levels. Lung cancer cell membranes exhibit specific methadone binding sites different from the ones in rat brain membranes.

Liu et al. [13] used human colorectal and lung cancer cell lines and applied LDN as well as NTX with cyclophosphamide, gemcitabine, and oxaliplatin. They evaluated the gene expression profile of a cancer cell line after treatment with LDN and found that LDN resulted in specific changes to genes involved in cell cycle control, which were absent when doses were much higher. They also noticed that primed cells with LDN exhibit a higher cytotoxic effect, when exposed to the chemotherapy agents, mentioned above.

Published Clinical Experience of LDN in Oncology

Khan [1] presented a case report of successful treatment of adenoid cystic carcinoma of the tongue with LDN and vitamin D3. Rogosnitzky et al. [14] Presented two pediatric cases of hepatoblastoma treated with surgical resection and LDN demonstrating a promising safe and therapeutic modality. The first case has more than ten years disease-free survival and the second case more than five years disease-free survival.

A group of naturopathic physicians from Arizona [15] presented 3 cases of pancreatic carcinomas treated with intravenous Alpha-Lipoic Acid (ALA) 300 to 600 my two days per week and LDN 4.5 mg by mouth at bedtime plus a triple antioxidant regimen of oral ALA 600 mg per day, selenium 200 mcg twice daily, and silymarin 300 mg four time a day. The first patient improved serologically, physically, and symptomatically with a negative PET, normal CEA and CA 19-9 tumor markers, and 39 months living after her diagnosis. The second patient improved too with weight gain and negative imaging and serology studies five months after her initial visit, but then she quite her treatment and expired 14 months following initial diagnosis. The third case had better symptoms and inclusive pain-free and off pain killers. He was taken off LDN and became septic and expired 12 months after initial diagnosis.

A group reported eleven cases from France [16] and all patients had failed standard chemotherapy and were offered only palliative care by their oncologists. Karnofsky status was between 50 and 60 with a life expectancy between two and six months. Two were lung cancer, two of colon, one ovarian, one esophageal, one uterine sarcoma, one from the liver, one from parotid, one from prostate, and another one unknown primary site. They were treated with a combination of lipoic acid 600 mg IV, hydroxycitrate 500 oral three times a day, and LDN 5 mg oral at bedtime. The regimen had no toxicity, and the diseases were either stable or very slowly progressive, although two of them expired. So, the study suggests that targeting cancer metabolism with LDN and ALA may be a reasonable option for patients with advanced disease.

One study with 10 metastatic renal cell cancer patients [17], who had progressed on a previous immunotherapeutic treatment with IL-2 alone, were treated with the same doses of IL-2 (6 million lU/day subcutaneously for 6 days/week for 4 weeks) plus an oral administration of NTX at a dose of 100 mg every 2 days. The clinical response consisted of a partial response in 1 and a stable disease in 5 patients, whereas the other 4 patients progressed. Therefore, the percent of non-progressive disease was 6/10 (60%). Moreover, the mean lymphocyte increase achieved during IL-2 plus NTX was significantly higher ($P<0.05$) than that obtained during the previous treatment with IL-2 alone.

Medical Literature of Cases of Cancer treated with LDN and HDIVC

We reviewed the medical literature through www.pubmed.com and only one case found with HDIVC and LDN. Berkson& Calvo Riera[18] described a situation of a patient with stage IV renal cell carcinoma treated with HDIVC 25 to 50 g, every morning and IV ALA 300 to 600 mg every afternoon after a meal at the clinic plus LDN 4.5 mg at bedtime, oral triple antioxidant therapy protocol since August of 2010. After one week of therapy, he began to feel better than later, but by January of 2011, he gained 8 pounds, with better clinical picture and serial imaging studies (PET/CT scans and CT scan) on 2013, 2014, 2015, and 2017. He continues alive with no evidence of disease and in good health on his protocol at the time of the publication.

Our Experience

We have 5 cases so far using LDN in cancer patients since 2015 of which 3 are females and 2 are males. The age ranges from 48 to 85 years-old with a mean age of 70 but 67 for the females and 74 for the males. One male is from USA and one female is from South America, although the rest are from Puerto Rico. The three females have infiltrating ductal adenocarcinomas. One is receiving neoadjuvant hormonal therapy with Tamoxifen 20 mg oral daily plus HDIVC 50 gm weekly followed then by 25 gm monthly with LDN 4.5 mg orally at bedtime. She is currently receiving treatment with excellent response and tumor regression. She is refusing to have surgery because her tumor is almost gone. Theanother, two cases have been heavily treated before. The youngest one received

How to cite this article: Raúl H Morales-Borges, Nelmarie Álvarez-Rodríguez. Low-Dose Naltrexone in Combination with High-Dose Vitamin C in Cancer Patients: Our Experience and Medical Literature Review - it should be Reinforced in Our Practices of Integrative Oncology. Ann Rev Resear. 2018; 4(2): 555632.

TAC adjuvant regimen followed by Tamoxifen but had recurrent metastatic disease to bones and lungs, visited me for a second opinion for Integrative Regimen and received Gemcitabine IV plus Fulvestrant IM with Zoledronic acid IV together with Integrative Regimen of LDN 4.5 mg orally at bedtime and HDIVC 25 gm IV weekly, then once attained clinical and radiological remission after 6 months of diagnosed her recurrence, she was kept on LDN and HDIVC (25 gm IV monthly) which is still continuing on it. The oldest female patient has stage IV triple negative disease and failed to taxanes, anthracycline, and Carboplatin by another oncologist. She is currently on Pembrolizumab, HDIVC 25 gm every 2 weeks plus LDN 4.5 mg daily. Sue is tolerating with minimal toxicity and excellent performance status. One male patient has Castrate-Resistant Metastatic Prostate Cancer to pelvic and retro-peritoneal lymph nodes that failed to Abiraterone and Prednisone and is currently on The Integrative Regimen of LDN 4.5 mg daily plus oral Vitamin C 4000 daily. He is pain free, gaining weight, with excellent performance status. The second male patient has Squamous Cell Carcinoma of Pyriform Sinus (head and neck cancer) locally advanced who initially got Chemoradiotherapy regimen but another oncologist and did not complete it due to moderate to severe side effects. He refuses more treatment as well as surgery but accepted the Integrative Regimen of LDN and HDIVC. He has been on LDN 4.5 mg daily plus Vitamin C 50 gm IV every 2 with excellent clinical and radiological response for 6 months since initial visit to us.

Conclusion

LDN and HDIVC are a promising Integrative Regimen for cancer patients as demonstrated by the reviewed medical literature and by our experience. This is the second paper that showed the effectiveness of the combination and it should be use more frequently in our practices of Integrative Oncology not either in advanced cases as palliative therapy, but also as neoadjuvant therapy. The combination makes the cancer cell more susceptible to anti-cancer modalities and bring them a better quality of life and performance status. We encouraged the physicians to see the clinical therapeutic potential revealed by our team and other researchers.

References

1. Khan A (2014) Long-term remission of adenoid cystic tongue carcinoma with low dose naltrexone and vitamin D3-a case report. Oral Health Dent Manag 13(3): 721-724.
2. Li Z, You Y, Griffin N, Feng J, Shan F (2018) Low-dose naltrexone (LDN): A promising treatment in immune-related diseases and cancer therapy. Int Immunopharmacol 61: 178-184.
3. Brown N, Panksepp J (2009) Low-dose naltrexone for disease prevention and quality of life. Med Hypotheses 72(3): 333-337.
4. Gonzalez MJ, Miranda-Massari (2014) New Insights on Vitamin C and Cancer. Springer Briefs in Cancer Research. Springer.
5. Lunec J, Holloway KA, Cooke MS, Faux S, Griffiths HR, et al. (2002) Urinary 8-oxo-2'-deoxyguanosine: redox regulation of DNA repair in vivo? Free Radic Biol Med 33(7): 875-885.
6. Knowles HJ, Raval RR, Harris AL, Ratcliffe PJ (2003) Effect of ascorbate on the activity of hypoxia-inducible factor in cancer cells. Cancer Res 63(8): 1764-1768.
7. Nauman G, Gray JC, Parkinson R, Levine M, Paller CJ (2018) Systematic Review of Intravenous Ascorbate in Cancer Clinical Trials. Antioxidants 7(7): E89.
8. Zagon IS, McLaughlin PJ (1983) Naltrexone modulates tumor response in mice with neuroblastoma. Science 221(4611): 671-673.
9. Murgo AJ (1989) Modulation of murine melanoma growth by naloxone. Cancer Lett 44(2): 137-142.
10. Aylsworth CF, Hodson CA, Meites J (1979) Opiate antagonists can inhibit mammary tumor growth in rats. Proc Soc Exp Biol Med 161(1): 18-20.
11. Donahue RN, McLaughlin PJ, Zagon IS (2011) Low-dose naltrexone suppresses ovarian cancer and exhibits enhanced exhibition in combination with cisplatin. Exp Biol Med (Maywood) 236(7): 883-895.
12. Maneckjee R, Minna JD (1992) Nonconventional opioid binding sites mediate growth inhibitory effect of methadone on human lung cancer cells. Proc Natl Acad Sci USA 89(4): 1169-1173.
13. Liu WM, Scott KA, Dennis JL, Kaminska E, Levett AJ, et al. (2016) Naltrexone at low doses up-regulates a unique gene expression not seen with normal doses: Implications for its use in cancer therapy. Int J Oncol 49(2): 793-802.
14. Rogosnitzky M, Finegold MJ, McLaughlin PJ, Zagon IS (2013) Opioid growth factor (OGF) for hepatoblastoma: a novel non-toxic treatment. Invest New Drugs 31(4): 1066-1070.
15. Berkson BM, Rubin DM, Berkson AJ (2009) Revisiting the ALA/N (alpha-lipoic Acid/Low-Dose Naltrexone) Protocol for People with Metastatic and Nonmetastatic Pancreatic Cancer: A Report of 3 New Cases. Integr Cancer Ther 8(4): 416-422.
16. Schwartz L, Buhler L, Icard P, Lincet H, Steyaert JM (2014) Metabolic Treatment of Cancer: Intermediate Results of a Prospective Case Series. Anticancer Res 34(2): 973-980.
17. Lissoni P, Malugani F, Bordin V, Conti A, Maestroni G, et al. (2002) A new neuro immunotherapeutic strategy of subcutaneous low-dose interleukin-2 plus the long-acting opioid antagonist naltrexone in metastatic cancer patients progressing on interleukin-2 alone. Neuro Endocrinol Lett 23(3): 255-258.
18. Berkson BM, Calvo Riera F (2018) The Long-Term Survival of a Patient with Stage IV Renal Cell Carcinoma following an Integrative Treatment Approach Including the Intravenous Alpha-Lipoic Acid/Low-Dose Naltrexone Protocol. Integr Cancer Ther17(3): 986-993.

How to cite this article: Raúl H Morales-Borges, Nelmarie Álvarez-Rodríguez. Low-Dose Naltrexone in Combination with High-Dose Vitamin C in Cancer Patients: Our Experience and Medical Literature Review - it should be Reinforced in Our Practices of Integrative Oncology. Ann Rev Resear. 2018; 4(2): 555632.

How to cite this article: Raúl H Morales-Borges, Nelmarie Álvarez-Rodríguez. Low-Dose Naltrexone in Combination with High-Dose Vitamin C in Cancer Patients: Our Experience and Medical Literature Review - it should be Reinforced in Our Practices of Integrative Oncology. Ann Rev Resear. 2018; 4(2): 555632.