Low Dose Naltrexone in Cancer Prevention and Treatment

LDN Research Trust Conference

www.ldnresearchtrust.org

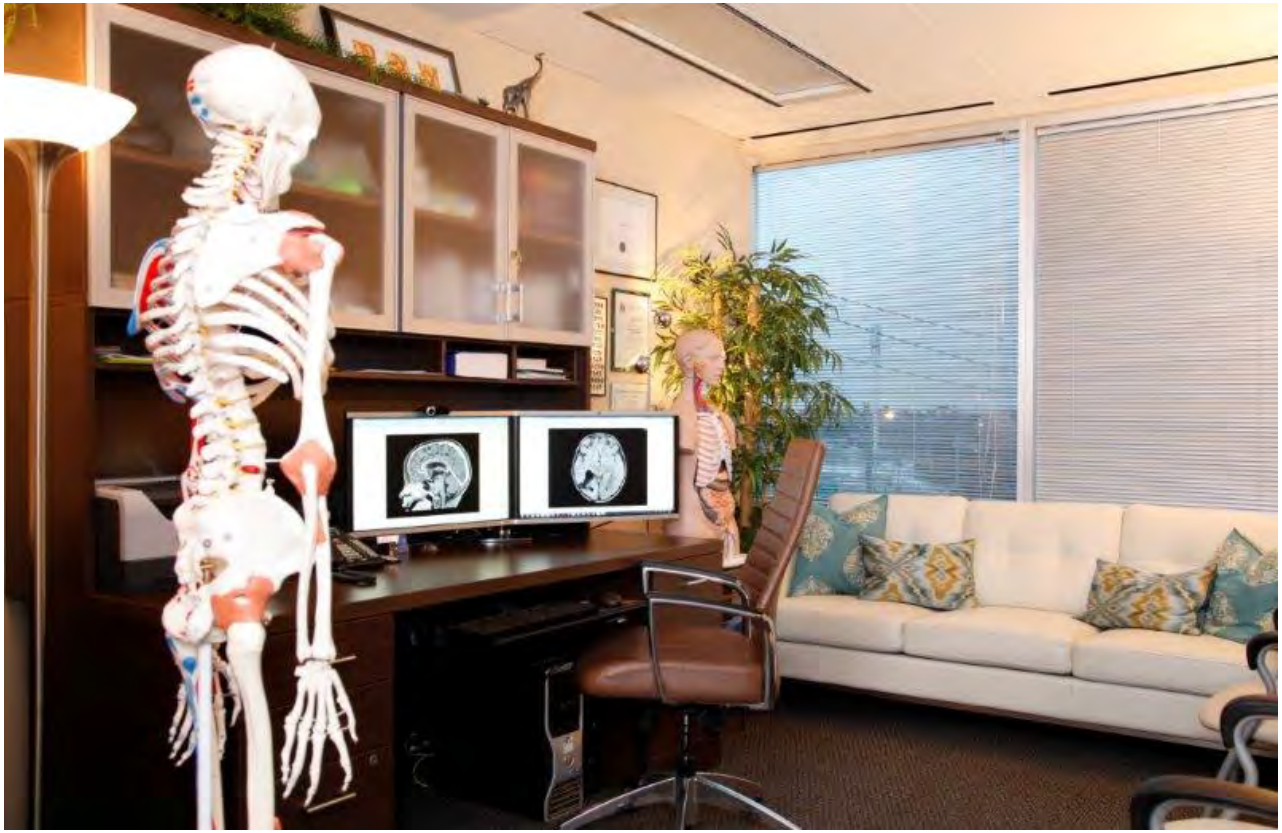
2018

Akbar Khan, M.D.

Disclosure

The presenter is the Medical Director of Medicor Cancer Centres Inc. where LDN is prescribed and dispensed for a fee, but without profit (by law). A family member of the presenter has ownership interest in the clinic.

Medicor Office – A Healing Environment

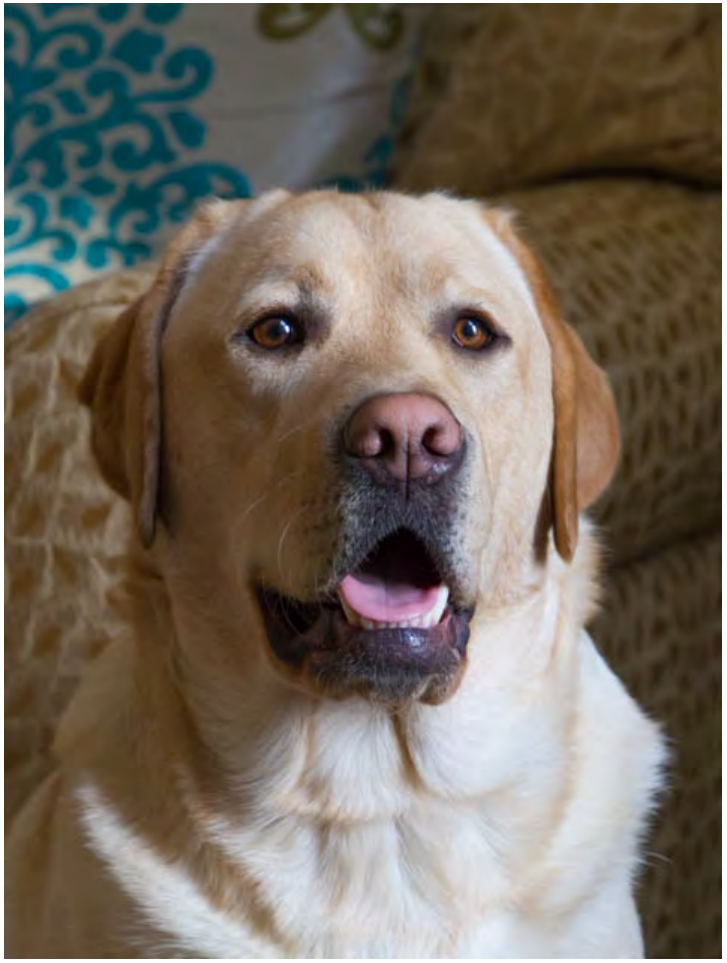


www.medicorcancer.com

Founded in 2006

MD / ND Working Together

Medicor Therapy Dog: Charlie



Rationale for Non-Toxic Therapy

- Most conventional cancer therapies are toxic, even non-chemo drugs
- Cytotoxic chemotherapy – immune damage, infection, clotting, new cancers
- Radiation – site-specific side eff, new cancers
- “Targeted” drugs – supposed to be safer?
- New immunotherapies – immune overstimulation and organ destruction

Rationale for Non-Toxic Therapy

Clin Oncol (R Coll Radiol). 2004 Dec;16(8):549-60.

The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies.

Morgan G[1], Ward R, Barton M.

⊕ Author information

Abstract

AIMS: The debate on the funding and availability of cytotoxic drugs raises questions about the contribution of curative or adjuvant cytotoxic chemotherapy to survival in adult cancer patients.

MATERIALS AND METHODS: We undertook a literature search for randomised clinical trials reporting a 5-year survival benefit attributable solely to cytotoxic chemotherapy in adult malignancies. The total number of newly diagnosed cancer patients for 22 major adult malignancies was determined from cancer registry data in Australia and from the Surveillance Epidemiology and End Results data in the USA for 1998. For each malignancy, the absolute number to benefit was the product of (a) the total number of persons with that malignancy; (b) the proportion or subgroup(s) of that malignancy showing a benefit; and (c) the percentage increase in 5-year survival due solely to cytotoxic chemotherapy. The overall contribution was the sum total of the absolute numbers showing a 5-year survival benefit expressed as a percentage of the total number for the 22 malignancies.

RESULTS: The overall contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults was estimated to be 2.3% in Australia and 2.1% in the USA.

CONCLUSION: As the 5-year relative survival rate for cancer in Australia is now over 60%, it is clear that cytotoxic chemotherapy only makes a minor contribution to cancer survival. To justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a rigorous evaluation of the cost-effectiveness and impact on quality of life is urgently required.

THE CONTRIBUTION OF CYTOTOXIC CHEMOTHERAPY TO LONG-TERM SURVIVAL IN ADULT CANCERS IS:

< 3%

"It is clear that cytotoxic chemotherapy only makes a **minor contribution to cancer survival**. To justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a **rigorous evaluation** of the cost-effectiveness and impact on quality of life is **urgently required." (2004)**

Rationale for Non-Toxic Therapy

Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial

Paula Mulvenna, Matthew Nankivell, Rachael Barton, Corinne Faivre-Finn, Paula Wilson, Elaine McColl, Barbara Moore, Iona Brisbane, David Ardron, Tanya Holt, Sally Morgan, Caroline Lee, Kathryn Waite, Neil Bayman, Cheryl Pugh, Benjamin Sydes, Richard Stephens, Mahesh K Parmar, Ruth E Langley

Summary

Background Whole brain radiotherapy (WBRT) and dexamethasone are widely used to treat brain metastases from non-small cell lung cancer (NSCLC), although there have been no randomised clinical trials showing that WBRT improves either quality of life or overall survival. Even after treatment with WBRT, the prognosis of this patient group is poor. We aimed to establish whether WBRT could be omitted without a significant effect on survival or quality of life.

Methods The Quality of Life after Treatment for Brain Metastases (QUARTZ) study is a non-inferiority, phase 3 randomised trial done at 69 UK and three Australian centres. NSCLC patients with brain metastases unsuitable for surgical resection or stereotactic radiotherapy were randomly assigned (1:1) to optimal supportive care (OSC) including dexamethasone plus WBRT (20 Gy in five daily fractions) or OSC alone (including dexamethasone). The dose of dexamethasone was determined by the patients' symptoms and titrated downwards if symptoms improved.

Published Online
September 4, 2016
http://dx.doi.org/10.1016/S0140-6736(16)30825-X
See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(16)31391-5

Northern Centre for Cancer Care, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
(P Mulvenna FRCR); Medical

LANCET
SEP 2016

IN NON-SMALL CELL LUNG CANCER SPREAD TO THE BRAIN, WHAT IS THE IMPROVEMENT IN SURVIVIAL AND/OR QOL?

Zero benefit

"The data from the whole trial population suggest that **WBRT can be omitted** and patients treated with Optimal Supportive Care alone, without an important reduction in either overall survival or quality of life." (PHASE 3 TRIAL 538 PATIENTS, THE LANCET, SEP 2016)

Why are we using ineffective therapies, harming patients and wasting $$$?

WE NEED A PARADIGM SHIFT

LDN

LDN - Mechanisms

- Off-label use of LDN as a cancer therapy was discovered by Dr. Bernard Bihari

Mechanism:

- Brief opiate receptor blockade creates a surge in endorphin levels including OGF, a cell growth regulator
- Block TLR4 signalling: modulates immune response

LDN - Mechanisms

- Liu, Dalgleish et al: 2016 new mechanisms of LDN action against cancer discovered
- *in vitro* study with human lung and colon adenocarcinoma cell lines
- LDN alters genes involved in cell cycle regulation
- LDN conc. 1nM and 10nM vs. regular naltrexone (micromolar conc.)

LDN - Mechanisms

- Paired immunoglobulin-like type 2 receptor A (PILRA) regulates immune system: upregulated
- Pro-apoptotic genes BAK1, BAD: upregulated
- Cycling of LDN was better: 2d treatment with 1d break = enhanced apoptosis
- Compared against regular doses of naltrexone: no benefits

LDN - Mechanisms

- LDN priming of cancer cells for 2d before chemo
- Cyclophosphamide, gemcitabine and oxaliplatin studied
- Result: modest improvement in cell kill
- Compared against regular doses of naltrexone: little benefit

Published Data - OGF

- Zagon et al. have studied OGF extensively
- Found to kill colon[1], pancreas[2], squamous cell[3], neuroblastoma[4], renal cell[5], triple neg. breast[6], ovarian cancers[7] (*in vitro*)
- Phase 1 human trial of i.v. OGF in 16 pancreatic cancer patients showed improved survival over standard 5-FU or gemcitabine chemo, with good pain control[8]

Published Data - LDN

- Very limited published human research
- Generic drug, too cheap? No R.O.I.
- Phase 2 breast cancer study – **terminated**[1]
- Phase 2 study of melanoma, prostate, renal cell, **terminated**[1]

1. www.clinicaltrials.gov

Published Data - LDN

- Phase 2 study of gliomas, when combining LDN with chemo / radiation , conducted in USA
  Results: not published? data not analyzed? Data is available on clinicaltrials.gov
  improved QOL with LDN[1]
- Phase 2 randomized trial with 89 leukemia patients conducted in Iran
  Results: **improved QOL** with LDN[2] ($p<0.05$)

Published Data - LDN

- Berkson et al. published convincing case reports of successful long-term treatment of **pancreatic cancer** using LDN + alpha lipoic acid[1]
- Responses confirmed by PET scans
- Berkson also published a case of **B-cell lymphoma** response to LDN[2]

Published Data - LDN

- **New paper** by Berkson et al. published Dec 2017
- convincing case report of successful treatment of stage 4 **renal cell carcinoma** using LDN, iv alpha lipoic acid, iv vitamin C, hydroxycitrate and healthy lifestyle program
- Responses confirmed by PET scans over 9 years
- No concurrent conventional cancer therapy

Published Data - LDN

- Khan: 2014 case report of successful long-term complete remission of **adenoid cystic tongue cancer** using LDN + high dose Vitamin D[1]
- Response confirmed by MRI scans
- **2018 update**: patient stopped LDN after 5 years on the advice of his ENT doctor and remains cancer-free

Common Side Effects

OGF

- No significant side effects
- Hypotension or dizziness after infusion is possible

LDN

- Insomnia and intense dreams are common (easily treated by morning LDN dosing or adding a natural sleeping pill)

Good Side Effects / Benefits

- Improved mood
- Enhanced sense of well-being
- Many others (not well documented yet)

Drug Interactions

- OGF – none known
- LDN – opiate antagonist, **do not use together** with opiates

Never use LDN in patients on continuous opiate medication! (time release oral, pain pump, pain patch, methadone). **Acute opiate withdrawal!**

Ok to use with intermittent short-acting daytime opiates, no opiate at bedtime. Opiate won't work.

Sample LDN Protocol (adult)

- Escalating dose is preferable:
- Start 2mg at bedtime, increase to max 4 or 4.5mg gradually over 1 - 3 weeks according to side effects (insomnia/dreams)
- Do not go over 5mg
- Given at bedtime for max. effect
- We start with 1mg caps and 1mg/ml oral liquid, to allow dose escalation

Sample LDN Protocol (adult)

- May need treatment for insomnia
- Consider natural medications with proven anti-cancer effects for synergism and improved sleep
- Honokiol (magnolia extract)
- Melatonin (up to 20mg at bedtime)
- Can use benzodiazepine like lorazepam (avoid)
- Morning dosing an option (less powerful?)

Sample LDN Protocol (pediatric)

- Correct dose in children is not known
- Estimated target: **0.1mg/kg/day at bedtime**
- Start at ½ of this and increase gradually as in adults
- Use naltrexone flavoured oral liquid 1mg/ml, and a 1ml syringe for measuring
- Must be flavoured correctly (bitter otherwise)
- Ask a skilled compounding pharmacist

Our Experience

- > 400 cancer patients treated with LDN
- Experience with LDN over a period of 10 years
- Most patients received concurrent non-toxic therapy (e.g. natural medicines) so collection of specific response data on 400 patients is difficult
- Carefully selected case reports are more useful

CASE PRESENTATION

Case 1 – Breast Cancer

- 29 year old female felt a breast mass
- Biopsy-proven breast cancer (IDC) , ER+, HER2-
- Surgery (partial mastectomy)
- Declined adjuvant chemo/radiation
- Started natural therapy with vitamin C 1000mg twice a day and vitamin D 2000U/d
- CTC count showed 650 live cancer cells/ml of blood

Case 1 – Breast Cancer

- Cancer markers with natural therapy:
- CA15-3 = 10 CEA = 0.3 (both normal)
- Started LDN, usual dosing
- Added metformin 500mg 3 times a day
- Added honokiol 2 x 500mg 3 times a day
- CTC count fell from 650 to 250 after 3 months
- Cancer markers also fell:
- CA15-3 = 5 CEA = 0.2

Case 2 – small bowel cancer

- 56 year old female with small bowel cancer
- Prior surgery, biopsy-proven
- Lung and liver metastases, responded to chemotherapy (partial response)
- Chemo stopped, started LDN with natural medicines per naturopathic doctor

Case 2 – small bowel cancer

- CT scan after 6 mo. of LDN: shrinkage of metastases
- CT scan after 9 mo. of LDN: stable disease
- CT scan after 12 mo. of LDN: mild re-growth noted
- No side effects of therapy

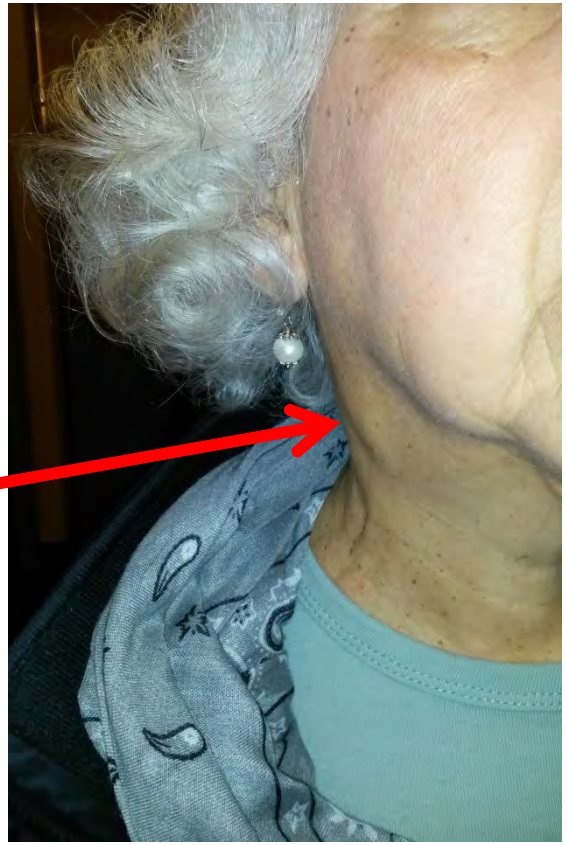
Case 3 - SCC

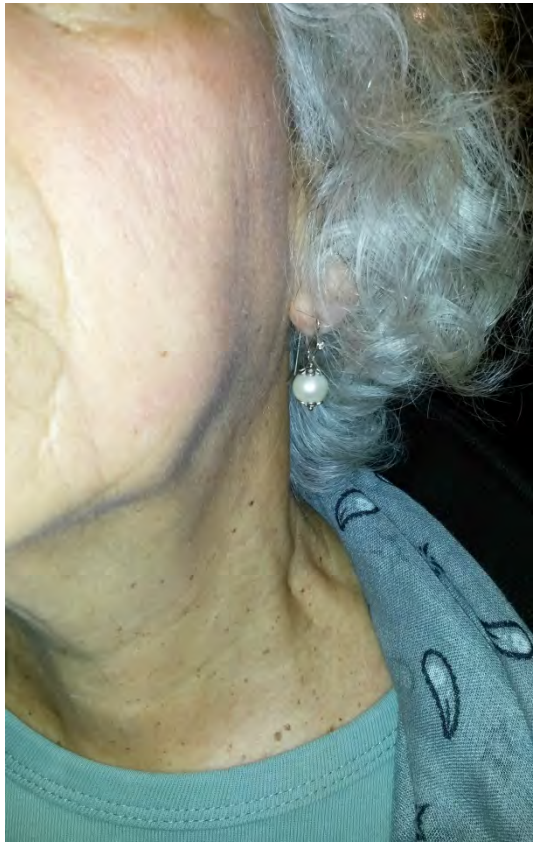
- 65 year old female with oropharyngeal squamous cell ca (right tonsillar)
- Type II DM
- Prior natural therapies e.g. IVC, cancer growth
- 7 x 3 cm tumour
- Dichloroacetate (DCA) + LDN 4mg at bedtime + vitamin D + metformin

Case 3 - SCC

- DCA stopped after 2 months due to mild side effects, LDN continued
- Shrinkage of tumour visually and by ultrasound
- Continued LDN + vit D + metformin
- Reduced to 3.2 x 2.4cm, **no growth for 3 years**
- New very poor glucose control (HBA1C = 14%, normal < 5.5%) only then was mild growth seen on ultrasound

Case 3 - SCC





Case 4 – TCC bladder

- 70 year old male with bladder cancer (transitional cell carcinoma)
- Standard therapy: excision / cautery “TURBT”
- Recurrent tumours
- Tried DCA therapy, cancer grew back
- Changed over to LDN, added honokiol for sleep and for anti-cancer effects

Case 4 – TCC bladder

- Reduction of cancer proven by ultrasound and cystoscopy
- Small red area visible on cystoscopy, no tumour
- Atypical cells on urine cytology, not clearly identified as cancer
- BCG given by urol: **latest cysto is clear**
- Remains on LDN for **4 yrs, no recurrence**

Case 5 – colon cancer

- 53 year old male with cancer of the sigmoid colon
- History of ulcerative colitis, cancer diagnosed due to routine investigation of rectal bleeding
- Tumour seen on colonoscopy, biopsy proven
- Localized disease, patient refused surgery due to fear of complications
- Started LDN + honokiol to help sleep + reduce anxiety

Case 5 – colon cancer

- CEA was increasing pre-LDN
- Patient noted improvement in colitis symptoms within weeks of starting LDN (less cramps, diarrhea)
- CEA began to fall after 4 mo. of LDN therapy
- CEA checked monthly:
- 9.3 - 8.0 - 7.1 - 6.1 - 6

Case 5 – colon cancer

- CEA stabilized between 6 and 7 (normal < 5)
- Repeat colonoscopy confirmed no disease progression
- On LDN therapy for over 1 year, still refused surgery
- Traveling for 3 months, ran out of LDN
- Rapid progression, invasion of tumour into bladder, stool in urine, increased CEA

Case 6 - Published

Long-Term Remission of Adenoid Cystic Tongue Carcinoma with Low Dose Naltrexone and Vitamin D3 – A Case Report

Akbar Khan

Medical Director, Medicor Cancer Centres Inc. 4576 Yonge St., Suite 301 Toronto, ON M2N 6N4, Canada.

Abstract

Naltrexone (ReVia®) is a long-acting oral pure opiate antagonist which is approved for the treatment of alcohol addiction as a 50mg per day tablet. The mechanism of action is complete opiate blockade, which removes the pleasure sensation derived from drinking alcohol (created by endorphins). Low Dose Naltrexone ("LDN") in the range of 3-4.5 mg per day has been shown to have the opposite effect – brief opiate receptor blockade with resulting upregulation of endogenous opiate production. Through the work of Bihari and Zagon, it has been determined that the level of the endogenous opiate methionine-enkephalin is increased by LDN. Met-enkephalin is involved in regulating cell proliferation and can inhibit cancer cell growth in multiple cell lines. Increased met-enkepahlin levels created by LDN thus have the potential to inhibit cancer growth in humans. Phase II human trials of met-enkephalin, case reports published by Berkson and Rubin, and the clinical experience of Bihari confirmed the potential role of LDN in treating pancreatic and other cancers. However, large scale trials are lacking and are unlikely to be funded given the current non-proprietary status of naltrexone. A case report is presented of successful treatment of adenoid cystic carcinoma as further evidence of LDN's potential as a unique non-toxic cancer therapy.

Key Words: Naltrexone, Cancer, Adenoid cystic, Vitamin D

Introduction

Naltrexone (ReVia®) is a long-acting oral pure opiate antagonist which is approved for the treatment of alcohol addiction in 50mg per day dosing [1]. The mechanism of action is complete opiate blockade, which removes the pleasure sensation derived from drinking alcohol (created by endorphins). Dr. Bernard Bihari, a neurologist who practiced

Case Presentation

A 58 year old male (Mr. Michel Charest from Montréal, Québec) presented to his family doctor with new swallowing problems, hemoptysis and nausea. There was a history of smoking 1/2 pack of cigarettes per day for about 15 years, alcohol intake of 2 standard drinks per day, high cholesterol and a remote history of jaundice. The only medication taken was atorvastatin. The

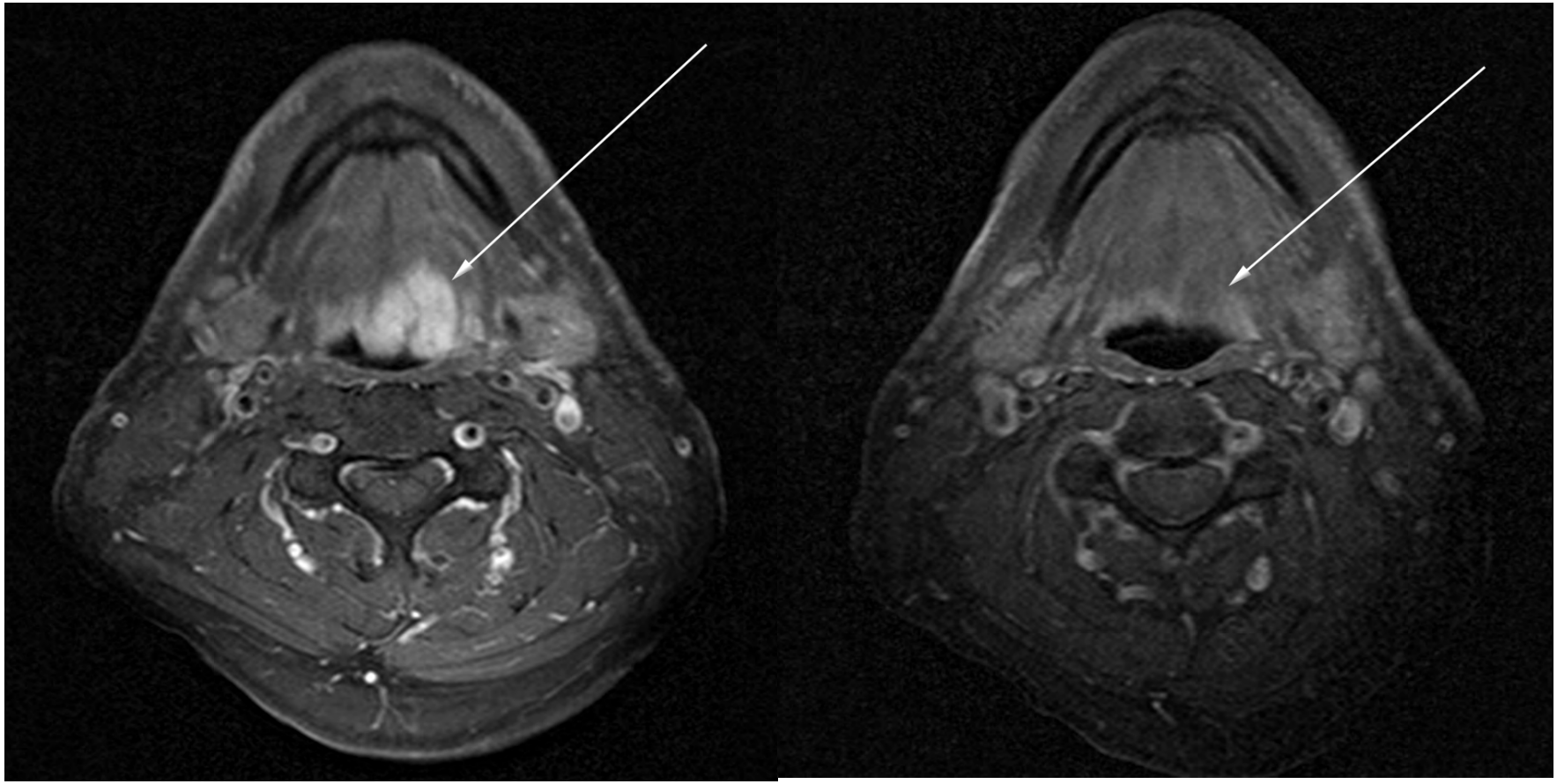
Case 6 – ACC tongue

- 60 year old male, adenoid cystic cancer at tongue base, no node mets (MRI), ~3cm dia
- Told to have radical surgery, glossectomy + laryngectomy + chemo/radiation
- Patient refused due to poor expected quality of life (QOL) post-op
- Chose LDN over possibly curative surgery

Case 6 – ACC tongue

- Started LDN 3mg at bedtime
- Added vitamin D 10,000U per day
- Increased LDN to 4.5mg at bedtime
- No side effects
- Mass stabilized over subsequent months, then gradual regression
- Vitamin D decr to 5,000U per day (level high)
- MRI after 2 years – complete remission

Case 6 - MRI



Case 6 – ACC tongue

- Patient remains in **complete remission over 5 years** after the start of LDN therapy
- Stopped LDN after 5 yrs, just on vitamin D
- Remains cancer-free
- Full publication in the journal Oral Health and Dental Management can be viewed on our website: www.medicorcancer.com

LDN as Cancer Prevention?

Low-Dose Naltrexone for Disease Prevention and Quality of Life

Med Hypotheses. 2009 Mar;72(3):333-7. PMID: 19041189

"Accumulating evidence suggests that LDN can promote health supporting immune-modulation which may reduce various oncogenic and inflammatory autoimmune processes."

LDN as Cancer Prevention?

The Use of Low-Dose Naltrexone (LDN) as a Novel Anti-Inflammatory Treatment for Chronic Pain

Clin Rheumatol. 2014 Apr;33(4):451-9 PMID: 24526250

"We review the evidence that LDN may operate as a novel anti-inflammatory agent in the central nervous system, via action on microglial cells."

LDN as Cancer Prevention?

Opioid growth factor and low-dose naltrexone impair central nervous system infiltration by CD4 + T lymphocytes in established EAE, a model of multiple sclerosis.

Exp Biol Med (Maywood). 2016 Jan;241(1):71-8 PMID: 26202376

"CNS-infiltrating CD4(+) T cells are diminished with exogenous OGF or intermittent blockade with LDN administration."

LDN as Cancer Prevention?

Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A Pilot Study

Pain Med. 2009 May-Jun;10(4):663-72. PMID: 19453963

"Individuals with higher sedimentation rates (indicating general inflammatory processes) had the greatest reduction of symptoms in response to low-dose naltrexone."

LDN as Cancer Prevention?

- Chronic inflammation plays a role in the development of cancer
- Higher risk of colon cancer with inflammatory bowel disease (Crohn's/colitis)
- Higher risk of esophageal cancer with chronic acid reflux causing inflammation
- Chronic H. pylori infection / inflammation increases gastric cancer risk

LDN as Cancer Prevention?

- LDN reduces harmful inflammation
- Chronic inflammation is associated with increased cancer risk
- Therefore chronic use of LDN in inflammatory conditions may reduce cancer risk
- Theoretical, no human prevention data yet
- Study to prove would be costly, but LDN is cheap and safe

LDN Summary

- LDN is best used for cases of cancer with low disease burden, prognosis > 3 months (our experience)
- Expect LDN to take some time to work (allow at least 3 mo.) – but may be faster
- LDN is more appropriate for low grade / slow growing cancers
- LDN is useful for elderly patients with cancer who may not tolerate other drugs
- Honokiol is a nice adjunct to LDN

www.prevent-cancer.ca

processes) had the greatest reduction of symptoms in response to low-dose naltrexone."

BMC Immunology

Endogenous Opioid Inhibition of Proliferation of T and B Cell Subpopulations in Response to Immunization for Experimental Autoimmune Encephalomyelitis

"OGF or LDN repress proliferation of CD4+ and CD8+T cells and B220+ B lymphocytes in the spleen and lymph nodes of immunized mice within a week of immunization."

"These data provide novel mechanistic pathways underlying the efficacy of OGF and LDN therapy for MS."

OHDM

Long-Term Remission of Adenoid Cystic Tongue Carcinoma with Low Dose Naltrexone and Vitamin D3 – A Case Report

"At the time of this writing, the patient has been re-assessed by the otolaryngologist who

67% had improved with mild disease activity...at the end of the study. Systemic and social quality of life improved with naltrexone treatment (p=0.035)."

INTEGRATIVE CANCER THERAPIES

Reversal of Signs and Symptoms of a B-Cell Lymphoma in a Patient Using Only Low-Dose Naltrexone

"We believe that by the mechanisms presented herein, LDN demonstrates significant potential to increase disease-free as well as overall survival in people with FL [follicular lymphoma]."

medical hypotheses

Low-Dose Naltrexone for Disease Prevention and Quality of Life

"Accumulating evidence suggests that LDN can promote health supporting immune-modulation which may reduce various oncogenic and inflammatory autoimmune processes."

"...it may also have a role in promoting stress resilience, exercise, social bonding, and

arthritis, polymyalgia rheumatica, and lupus, may benefit from LDN."

MULTIPLE SCLEROSIS JOURNAL
Formerly Multiple Sclerosis

A Pilot Trial of Low-Dose Naltrexone in Primary Progressive Multiple Sclerosis

"A significant reduction of spasticity was measured at the end of the trial."

"Our data clearly indicate that LDN is safe and well tolerated in patients with PPMS."

INTEGRATIVE CANCER THERAPIES

Revisiting the ALA/N (a-Lipoic Acid/Low- Dose Naltrexone) Protocol for People With Metastatic and Nonmetastatic Pancreatic Cancer: A Report of 3 New Cases

[Patient #1] GB was declared to be in radiological remission by PET surveillance... At the time of this writing, 39 months after her diagnosis, GB continues with her treatment plan and has no signs of pancreatic disease.[Patient #2] "...6 months following the initiation of therapy, her PET scan failed to demonstrate disease

Non-Toxic Therapy Summary

- There are many non-toxic cancer therapies
- LDN is one of the gentlest and safest
- Help spread the word
- Inform and educate your doctor:

Present the published research!


THANK YOU!
LAMAR
Coca-Cola
VECTOR
PIN UP
O'Reilly
KOBALT
LVMS.com
DREAM RACING
11
DREAM RACING

LDN 2018 Conference Presentation

By Dr Akbar Khan