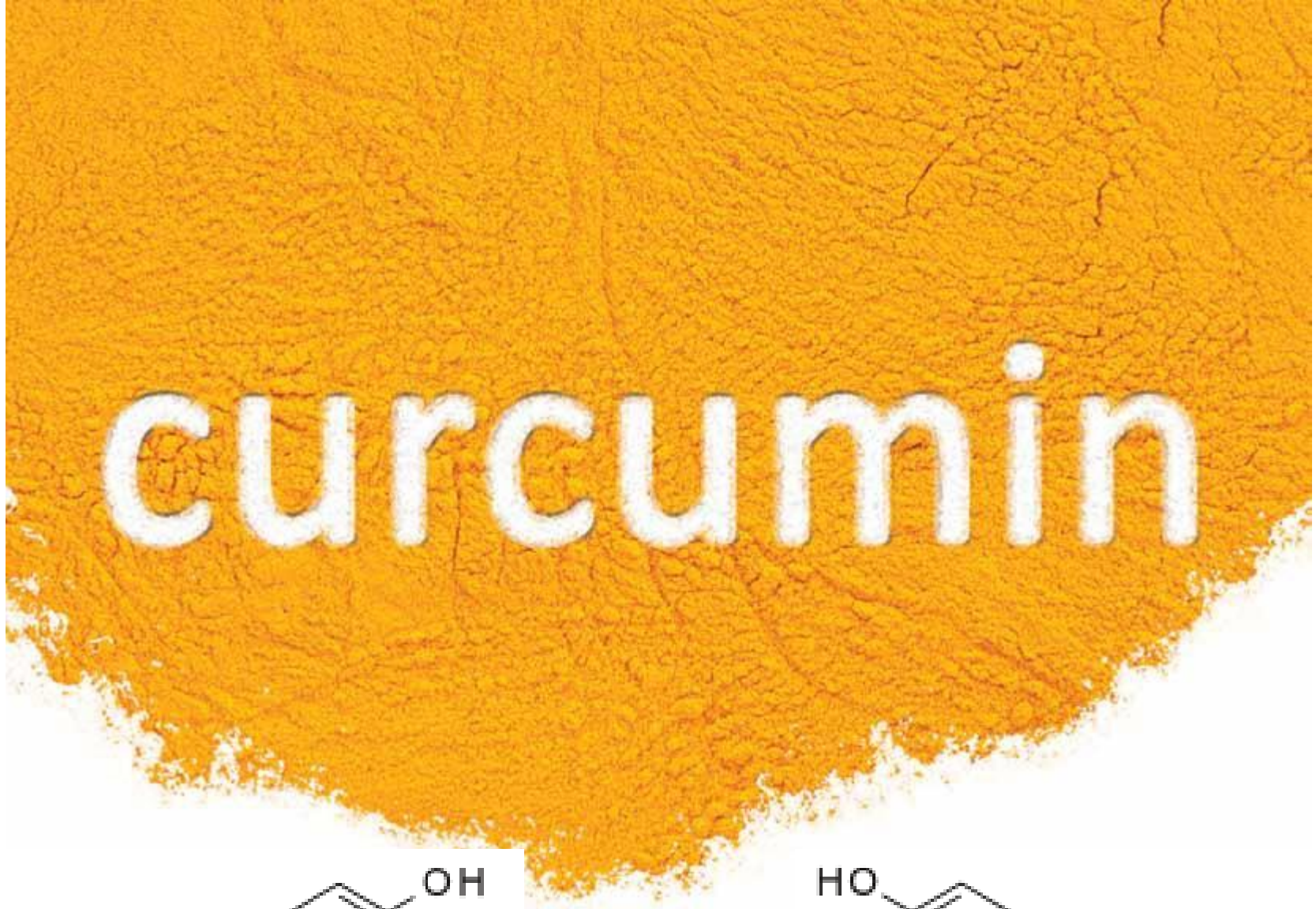
Novel IV Agents in Oncology:

Curcumin IV & TM Chelation

Virginia Osborne ND and Brenden Cochran, ND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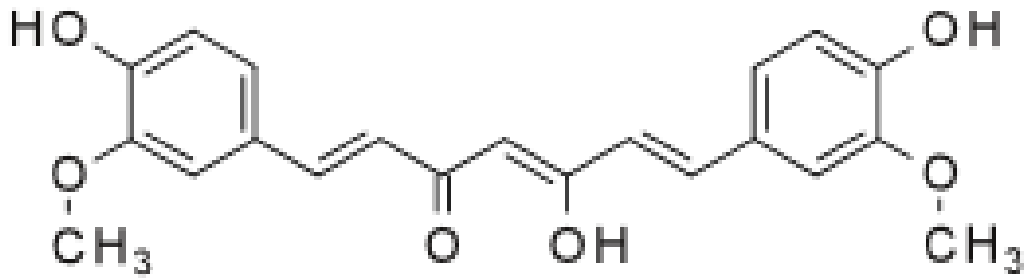
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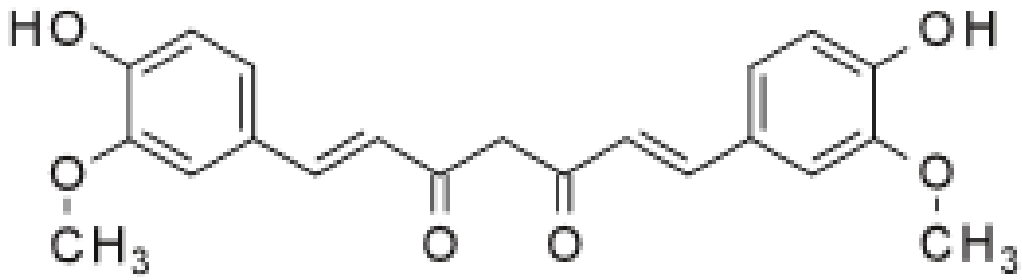
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Curcumin

Background: Because a role for nuclear factor-κB (NF-κB) has been implicated in the pathogenesis of pancreatic cancer, this transcription factor is a potential target for treatment of this devastating disease. Curcumin (diferuloylmethane) is a phytochemical with potent NF-κB-inhibitory activity. It is pharmacologically safe, but its bioavailability is poor after oral administration.

Methods: We encapsulated curcumin in a liposomal delivery system that would allow intravenous administration. We studied the *in vitro* and *in vivo* effects of this compound on proliferation, apoptosis, signaling and angiogenesis using human pancreatic cancer cells.

Kurzrock R. , Li L. Liposome-encapsulated curcumin: in vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis. General Poster Session, Gastrointestinal (Noncolorectal) Cancer. Abstract No: 4091 *Journal of Clinical Oncology*, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 4091

Curcumin

Conclusions: Liposomal curcumin downregulates the NF-κB machinery, suppresses growth, and induces apoptosis of human pancreatic cells, *in vitro*. Antitumor and anti-angiogenesis effects are observed *in vivo*. **Our experiments provide a biologic rationale for treatment of patients suffering from pancreatic cancer with this nontoxic phytochemical encapsulated in liposomes for systemic delivery.**

Kurzrock R. , Li L. Liposome-encapsulated curcumin: in vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis. General Poster Session, Gastrointestinal (Noncolorectal) Cancer. Abstract No: 4091 *Journal of Clinical Oncology*, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 4091

Curcumin

Abstract

Curcumin (diferuloylmethane) is a polyphenol derived from the Curcuma longa plant, commonly known as turmeric. Curcumin has been used extensively in Ayurvedic medicine for centuries, as it is nontoxic and has a variety of therapeutic properties including anti-oxidant, analgesic, anti-inflammatory and antiseptic activity. **More recently curcumin has been found to possess anti-cancer activities via its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis and metastasis.** Curcumin has shown anti-proliferative effect in multiple cancers, and is an inhibitor of the transcription factor NF- B and downstream gene products (including c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF-a, interleukins and MMP-9).

Wilken et al. Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Molecular Cancer 2011, 10:12

Curcumin

In addition, curcumin affects a variety of growth factor receptors and cell adhesion molecules involved in tumor growth, angiogenesis and metastasis. Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide and treatment protocols include disfiguring surgery, platinum-based chemotherapy and radiation, all of which may result in tremendous patient morbidity. As a result, there is significant interest in developing adjuvant chemotherapies to augment currently available treatment protocols, which may allow decreased side effects and toxicity without compromising therapeutic efficacy. Curcumin is one such potential candidate, and this review presents an overview of the current in vitro and in vivo data supporting its therapeutic activity in head and neck cancer as well as some of the challenges concerning its development as an adjuvant chemotherapeutic agent.

Wilken et al. Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Molecular Cancer 2011, 10:12

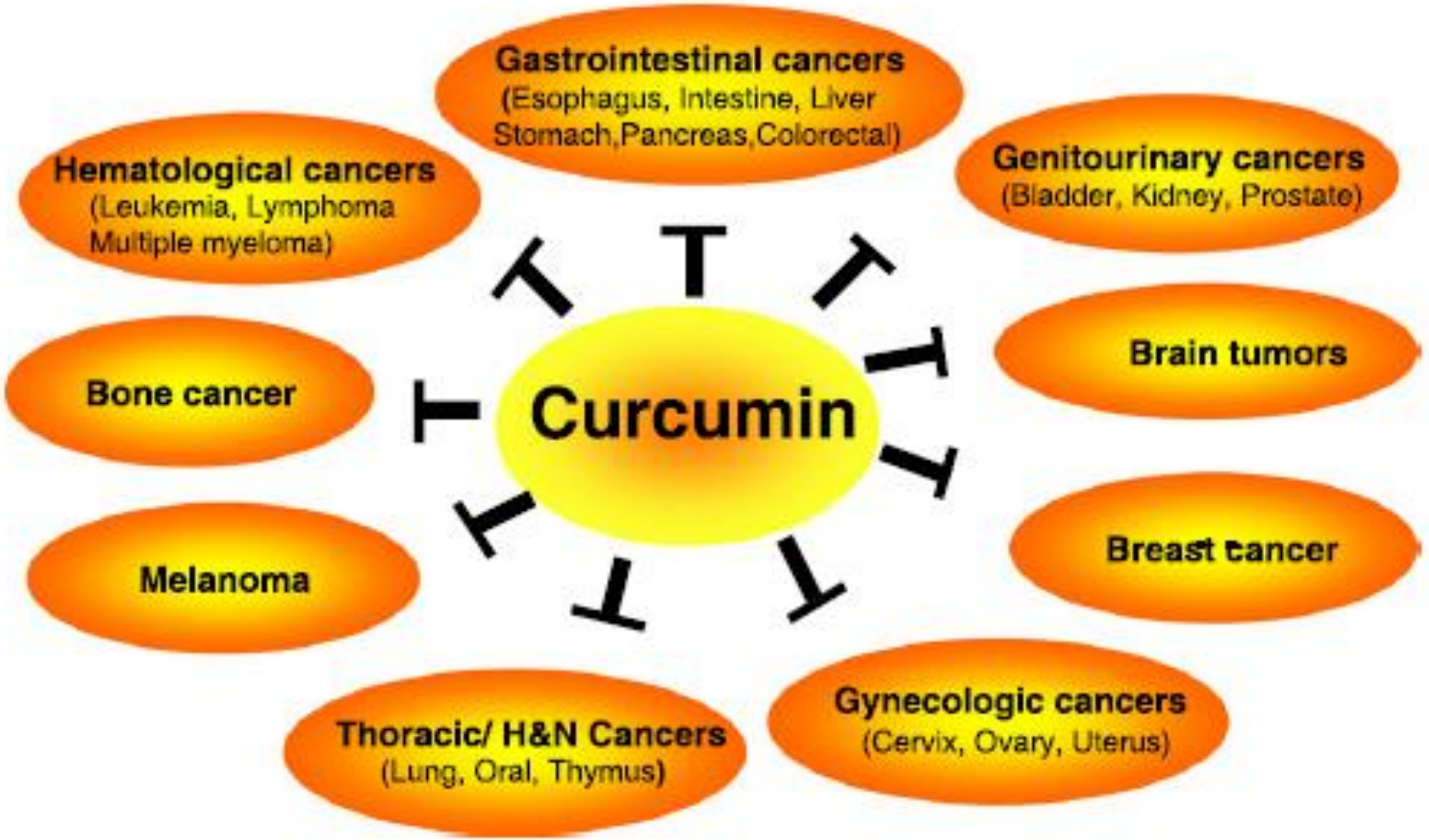


Fig. 3. Various cancers against which curcumin has potential for prevention and treatment.

Chen, C. et. al. An in vitro study of liposomal curcumin: Stability, toxicity and biological activity in human lymphocytes and Epstein-Barr virus-transformed human B-cells. International Journal of Pharmaceutics Vol. 366, No. 1, pages 133-139 (2009) DOI: 10.1016/j.ijpharm.2008.09.009

Curcumin is a multi-functional and pharmacologically safe natural agent. Used as a food additive for centuries, it also has anti-inflammatory, anti-virus and anti-tumor properties. We previously found that it is a potent inhibitor of cyclosporin A (CsA)-resistant T-cell co-stimulation pathway. It inhibits mitogen-stimulated lymphocyte proliferation, NF@kB activation and IL-2 signaling. In spite of its safety and efficacy, the in vivo bioavailability of curcumin is poor, and this may be a major obstacle to its utility as a therapeutic agent.

Liposomes are known to be excellent carriers for drug delivery. In this in vitro study, we report the effects of different liposome formulations on curcumin stability in phosphate buffered saline (PBS), human blood, plasma and culture medium RPMI-1640+10% FBS (pH 7.4, 37^oC). Liposomal curcumin had higher stability than free curcumin in PBS. Liposomal and free curcumin had similar stability in human blood, plasma and RPMI-1640+10% FBS.

Chen, C. et. al. An in vitro study of liposomal curcumin: Stability, toxicity and biological activity in human lymphocytes and Epstein-Barr virus-transformed human B-cells. International Journal of Pharmaceutics Vol. 366, No. 1, pages 133-139 (2009) DOI: 10.1016/j.ijpharm.2008.09.009

We looked at the toxicity of non-drug-containing liposomes on ^3H-thymidine incorporation by concanavalin A (Con A)-stimulated human lymphocytes, splenocytes and Epstein-Barr virus (EBV)-transformed human B-cell lymphoblastoid cell line (LCL). We found that dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylglycerol (DMPG) were toxic to the tested cells. However, addition of cholesterol to the lipids at DMPC:DMPG:cholesterol=7:1:8 (molar ratio) almost completely eliminated the lipid toxicity to these cells.

Liposomal curcumin had similar or even stronger inhibitory effects on Con A-stimulated human lymphocyte, splenocyte and LCL proliferation. **We conclude that liposomal curcumin may be useful for intravenous administration to improve the bioavailability and efficacy, facilitating in vivo studies that could ultimately lead to clinical application of curcumin.**

IV Curcumin – Not all created equal:

- A significant difficulty in describing the infusion of curcumin is the variety of potential forms of infusion product compounded. This paper describes mainly the solution form (3 below). We have additionally used form “2” below and find it more phlebogenic. No extrapolation of the clinical data presented herein should be made to forms other than a true solution of curcumin (“3” below).

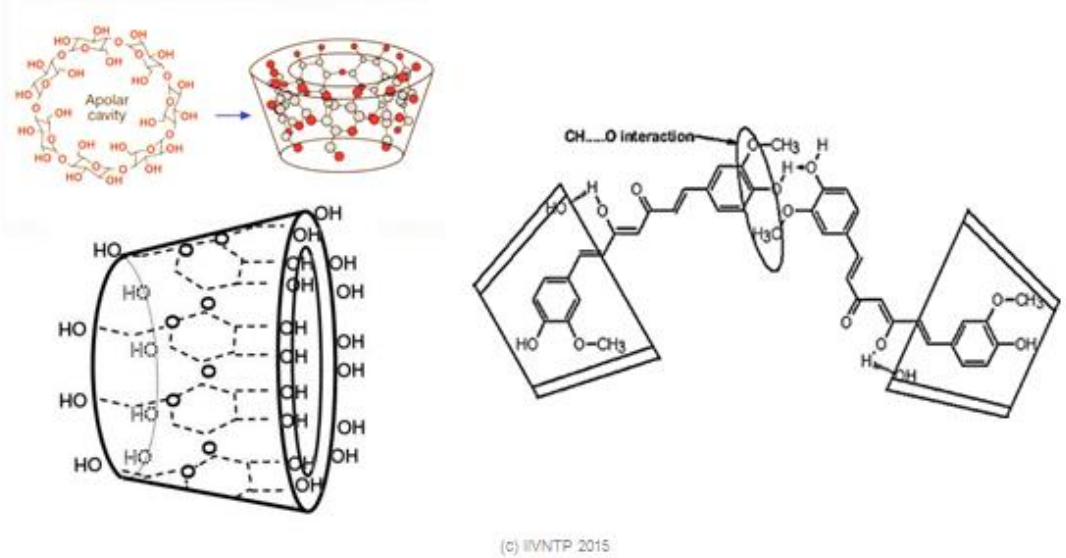
[1] Lipid (in a phospholipid Liposphere). Very hard to make properly and may be quite effective. Dripped slow like phosphatidylcholine IV.

[2] Curcumin in Cyclodextrin. Acts like the lipospheric form. Faster administration is possible but still a phlebitis potential if run too quickly.

[3] True Solution of Curcumin: Stabilized with a non-bound agent for solubility. Infusion rate is slow but is very vein tolerant. We are running kinetic studies now and have a few very positive outcomes. This is the form we currently infuse.

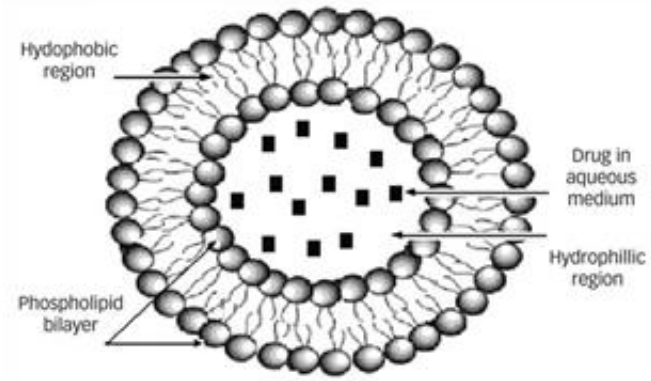
[4] Water Soluble solution. Highly alkaline to the point if not dilute will cause significant phlebitis and pH changes.

INTRAVENOUS CURCUMIN CYCLODEXTRIN:



True Solution Form

INTRAVENOUS CURCUMIN LIPOSPHERE:



Curcumin IV Issues:

- Reactions:
  - 1 anaphylactic or anaphylactoid observed to date.
  - Some transient ‘manic’ symptoms in a minority of patients.
  - Peripheral heat and hand foot itching has happened at doses above 20 mg/mL in a minority of patients. Duration of 1-2 days.
  - Transient (lasting seconds to minutes) central chest heat feeling.
  - Skin rash, redness, dizziness all reversed with a hydration IV of 500 mL NS
- Variable dosing for different purposes:
  - Anti-tumor effect as a monotherapy likely at 20 – 40 mg/Kg
  - Cytokine manipulation effect may occur at 100 – 500 mg total

Dilution

- Many of the reactions appear to not occur with better dilution of the curcumin.
- Our experience has shown that curcumin should not be administered at a greater dilution than 100 mg in 100 mL of saline or D5W.
- Most patients tolerate 400-500 mg in a 500 mL IV bag / 800 – 1000 mg per 1 Liter bag.

Administration Speed

- Speed is variable and based on patient tolerance.
- At 20 – 40 mg / Kg doses we find the following:
  - At the above dilutions the first IV should run at 5 to 7 mL / minute.
  - If tolerated then a rate of 7 – 10 mL / minute is often tolerated.
- At low dose (500 mg or less) we find:
  - Most doses 50 – 500 mg are given in 500 mL IV
  - AT this dose we run the IV at 7 - 10 mL / min.

Dosing

- For cytokine manipulation, autoimmune cases and potentially pain cases we find the following doses useful:
  - 1.5 – 10 mg / Kg
- For advanced cancer we have found much higher doses required. In the cases where we have had tumor response with curcumin as primary therapy we find the following doses useful:
  - Test doses at 5 – 10 mg / Kg then escalate
  - Top end doses have required 30 – 40 mg/Kg for tumor response

Clinical Notes:

Screening:

- Intolerance to oral curcumin excludes use in the IV setting
- Lab studies:
  - CBC, Chemistry panel (Metabolic panel including electrolytes, bilirubin, AST/ALT, eGFR/BUN/CRE)

Cautions:

- Curcumin is a GRAS (generally recognized as safe) food additive by the FDA. Multiple studies using
- High doses of oral curcumin in humans have shown incredible safety [2,3,4].
- Potential cautions (not contraindications) include:
- Patients who exhibit any Type-1 symptoms post – test IV dose
- Patients on **anticoagulants** [5]:
  - Employ caution in dosing and monitor for increased bleeding.
- Patients with known **gallbladder disease** [6,7] or Patients who develop post-IV diarrhea:
  - Question patients. Increased right upper quadrant or right shoulder pain, or significant post-IV diarrhea may indicate a decrease in dose or discontinuation of therapy.

Observed Reactions: [8]

- 1 anaphylactic or anaphylactoid observed to date.
- Nausea and vomiting:
  - In a minority of patients receiving over 10 mg/kg doses a transient and self-limited syndrome of dizziness, nausea and often vomiting has been observed. In each case the patient observed a dizziness and nausea combination of symptoms followed by vomiting of what appeared to be bile within 2-4 hours of finishing the infusion.
  - In each case the patient reported feeling “much improved” after the vomiting.
  - The vomiting was limited to one session following the infusion.
  - No patients have elected to discontinue high dose curcumin IV due to this experience.

Observed Reactions: [8]

- In each case the nausea and vomiting was either a lone event or two events in a row and were not at the beginning of therapy (most were after three to five infusions). Most only happened once.
- Our approach has been to decrease the body weight dose and ramp back up again to the therapeutic dose if tolerated.
- The proposed mechanism based on patient observations and clinical correlation is an aggressive choloretic effect sometime after the initiation of the infusion series that leads to increased biliary activity, nausea and the other symptoms.
- We do now recommend that patients consume a fiber supplement for bile sequestration before, during and the evening of the infusion. Psyllium husk at 5-10 grams per dose or cholestyramine at 2-4 grams per dose (all usual dose and administration cautions observed).
- Although only one in 30-50 infusions at doses over 10 mg/kg have reported this occurrence it is advisable to notify patients of the possibility in higher dose infusions and take preventive precautions (hydration and oral bile sequestrants).

Observed Reactions: [8]

- Some transient ‘manic’ / euphoric symptoms during and after the IV for up to 2-4 hours in a minority of patients.
- Peripheral heat and hand foot itching has happened at doses above 20 mg/mL in a minority of patients. Duration of 1-2 days.
- Transient (lasting seconds to minutes) central chest heat feeling.
- Skin rash, redness, dizziness all reversed with a hydration IV of 500 mL NS
  - Protocol is to stop the curcumin infusion and start the NS IV via piggy-back line. Infuse until the reaction stops and then (in most cases) re start the curcumin at a slower rate.
  - These patients will require a higher dilution on their next curcumin infusion.

Curcumin

(All failed multiple therapies including high dose IVC as well as other Nat Rx)

62 yo female stage IV ovarian cancer

- Presentation with multiple nodes in the axilla, cervical, pelvic.
- Mass in the pelvis adnexa
- Imaging both with CT and Ultrasound
- CA-125 = 378.9 Dec 2015
- Exhausted many therapies, came in on PNC-27

Treatment included 1800 mg liposphere based curcumin twice weekly

- CA-125 reduced to 152.6, the lowest number during the end of March 2016
- Imaging ultrasound and CT showed reduction in mass/node size in all locations
- CA-125 then increased to 182.1 beginning of June 2016
- Tapered off therapy due to cost.
- CA-125 increased to 381.1 by beginning of August 2016
- CA-125 679.4 by end of August 2016
- Patient passed September 2017

Curcumin

81 yo male with stage IV duodenal cancer with liver metastasis.

- (5/2014) Initially declined chemotherapy and did Gerson therapy with another doctor
- (7/2014) Initiated FOLFOX and Avastin for 11 cycles
- Progression of disease after chemotherapy
- Started HDIVC treatment prior to visiting me. Disease progression present. (End 2015)
- Started HDIVC + ART. (Jun 2015). Noted slowing of disease but still progression after 2 months.
- Sept 2015 switched to curcumin, worked up to 1000 mg.
- Noted drastic improvement in energy levels, and mood.
- Disease stabilization seen on imaging end of Oct. 2015
- Patient concerned about cost and oncologist offers low dose chemotherapy as option.
- Nov. 2015 patient ends Curcumin due to cost and does chemotherapy.
- Unfortunately passed of septic infection after first infusion and never came recovered.

References:

[1] Kinetic data by Anand would indicate that a starting dose on 10 mg/Kg IV in a human would be both safe and likely yield therapeutic levels in the plasma.

[2] Lao CD, Ruffin MTt, Normolle D, et al. Dose escalation of a curcuminoid formulation. BMC Complement Altern Med. 2006;6:10.

[3] Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2001;21(4B):2895-2900.

[4] Sharma RA, Euden SA, Platton SL, et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin Cancer Res. 2004;10(20):6847-6854.

[5] Rasyid A, Rahman AR, Jaalam K, Lelo A. Effect of different curcumin dosages on human gall bladder. Asia Pac J Clin Nutr. 2002;11(4):314-318.

[6] Shah BH, Nawaz Z, Pertani SA, et al. Inhibitory effect of curcumin, a food spice from turmeric, on platelet-activating factor- and arachidonic acid-mediated platelet aggregation through inhibition of thromboxane formation and Ca2+ signaling. Biochem Pharmacol. 1999;58(7):1167-1172.

[7] Srivastava KC, Bordia A, Verma SK. Curcumin, a major component of food spice turmeric (Curcuma longa) inhibits aggregation and alters eicosanoid metabolism in human blood platelets. Prostaglandins Leukot Essent Fatty Acids. 1995;52(4):223-227.

[8] Anderson P, Cochran B. Personal experiences with the clinical use of intravenous curcumin. AMSA, BIORC and Private clinic data. Seattle Washington,2015

Quercetin

- Tyrosine Kinase Inhibition
- Immunomodulator
- Antioxidant
- Antiproliferative and Antimutagenic
- Apotototic
- Etc…

Graefe EU, Derendorf H, Veit M. Pharmacokinetics and bioavailability of the flavonol quercetin in humans. Int J Clin Pharmacol Ther. 1999 May;37(5):219-33. PMID: 10363620

Flavonoids are plant polyphenolic compounds present in the daily diet. Latest epidemiological studies point to a crucial role of the flavonol quercetin in the prevention of cardiovascular diseases. It is assumed that this protective effect derives from the antioxidative capacity which quercetin shows in in vitro experiments. The antiproliferative and antimutagenic activities in vitro have made it a candidate for clinical trials in cancer therapy. Quercetin is also regarded as a putative active compound in various phytopharmaceuticals. However, in vivo data on the disposition, absorption, bioavailability, and metabolism of quercetin after intravenous and oral administration in humans are scarce and contradictory. The pharmacokinetic parameters following intravenous injection were determined in two studies. The elimination half-life was reported to be 2.4 h and 0.7 h, the volume of distribution at steady-state was 92.6 l and 6.2 l, and total body clearance was 34.6 lxh(-1) and 28.1 lxh(-1), respectively. Absorption after oral administration ranged from 0 to over 50% of the dose. These inconsistencies can partly be attributed to a lack of highly sensitive and specific assay methodology. The data available so far are insufficient to clarify whether or not quercetin can be held responsible for any protective or curative effect observed after oral intake.

Vol. 2, 659–668, April 1996

Phase I Clinical Trial of the Flavonoid Quercetin: Pharmacokinetics and Evidence for *in Vivo* Tyrosine Kinase Inhibition[1]

David R. Ferry,[2] Anna Smith, Joy Malkhandi, David W. Fyfe, Philippa G. deTakats, David Anderson, Jim Baker, and David J. Kerr

tyrosine kinase activity, and evidence of antitumor activity was seen.

Clin Cancer Res 659:

Quercetin pharmacokinetics were described by a firstorder two-compartment model with a median t#{189}a of 6 mm and median t#{189}(1 of 43 mm. The median estimated clearance was 0.28 liter/minim2, and median volume of distribution at steady state was 3.7 liter/rn2. In 9 of 11 patients, lymphocyte protein tyrosine phosphorylation was inhibited following administration of quercetin at 1 h, which persisted to 16 h. In one patient with ovarian cancer refractory to cisplatin, following two courses of quercetin (420 mg/rn2), the CA 125 had fallen from 295 to 55 units/mI, and in another patient with hepatoma, the serum a-fetoprotein fell. **In conclusion, quercetin can be safely administered by i.v. bolus at a dose injection. The plasma levels achieved inhibited lymphocyte tyrosine kinase activity, and evidence of antitumor activity was seen.**

Zhi-ping Yuan, Li-juan Chen, Lin-yu Fan, et al. Clin Cancer Res 2006;12:3193-3199.

Purpose: Quercetin is a potent chemotherapeutic drug. Clinical trials exploring different schedules of administration of quercetin have been hampered by its extreme water insolubility. To overcome this limitation, this study is aimed to develop liposomal quercetin and investigate its distribution in vivo and antitumor efficacy in vivo and in vitro.

Experimental Design: Quercetin was encapsulated in polyethylene glycol 4000 liposomes. Biodistribution of liposomal quercetin i.v. at 50 mg/kg in tumor-bearing mice was detected by high-performance liquid chromatography. Induction of apoptosis by liposomal quercetin in vitro was tested.The antitumor activity of liposomal quercetinwas evaluated in the immunocompetent C57BL/6N mice bearing LL/2 Lewis lung cancer and in BALB/c mice bearing CT26 colon adenocarcinoma and H22 hepatoma. Tumor volume and survival time were observed. The mechanisms underlying the antitumor effect of quercetin in vivo was investigated by detecting the microvessel density, apoptosis, and heat shock protein 70 expression in tumor tissues.

Results: Liposomal quercetin could be dissolved in i.v. injection and effectively accumulate in tumor tissues. The half-time of liposomal quercetin was 2 hours in plasma. The liposomal quercetin induced apoptosis in vitro and significantly inhibited tumor growth in vivo in a dosedependent manner. The optimal dose of liposomal quercetin resulted in a 40-day survival rate of 40%. Quantitative real-time PCR showed that liposomal quercetin down-regulated the expression of heat shock protein 70 in tumor tissues. Immunohistochemistry analysis showed that liposomal quercetin inhibited tumor angiogenesis as assessed by CD31 and induced tumor cell apoptosis.

Conclusions: Our data indicated that pegylated liposomal quercetin can significantly improve the solubility and bioavailability of quercetin and can be a potential application in the treatment of tumor.

INTRAVENOUS QUERCETIN:

- Intravenous Quercetin has studied potential for increased bioavailability [1,2,4] as well as potent potential anti-tumor activity [4-5].
- Intravenous data in human subjects shows it to be tolerated and safe [1-3].
- Data available suggest multiple mechanisms of action in Tyrosine Kinase inhibition [4] as well as tumor growth suppression [5]. Two years of clinical use has revealed no adverse events when used under standard dose and administration guidelines [3].

Clinical Notes:

Dose: [1-4]

- Test dose at 1 mg/kg IV on the first day
- Subsequent doses could increase to 140 mg/kg if tolerated two times weekly in Normal Saline

Administration:

- Intravenous dosing via either a central or peripheral line.
  - Use a filtered line or add on filter set
- Carrier solutions:
  - Per compounding pharmacy instructions
- Rate of administration: 60 to 240 minutes as tolerated by the patient
  - Monitor for signs of nausea which can be the first sign of a non-tolerated dose [3]
  - For allergic / anaphylactic reaction treat per standard protocol.
- Other IV compatibility:
  - Generally incompatible with other IV solutions in the same IV container

Screening:

- Intolerance to oral Quercetin is a caution and may exclude use in the IV setting

- Lab studies:
  - CBC, Chemistry panel (Metabolic panel including electrolytes, bilirubin, AST/ALT/GGT, eGFR/BUN/CRE).

References:

1. Gugler R., Leschik M., Dengler H. J.Disposition of quercetin in man after single oral and intravenous doses. European Journal of Clinical Pharmacology 1975, Volume 9, Issue 2-3, pp 229-234

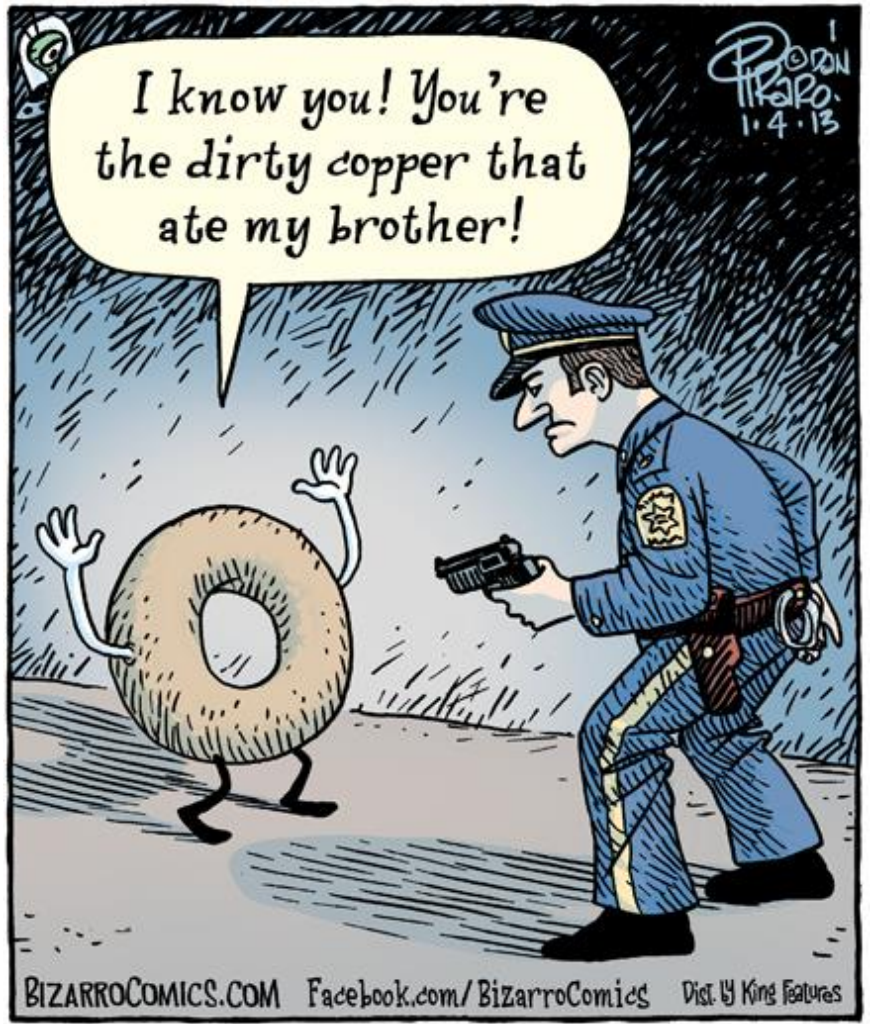
2. Graefe EU, Derendorf H, Veit M. Pharmacokinetics and bioavailability of the flavonol quercetin in humans. Int J Clin Pharmacol Ther. 1999 May;37(5):219-33. PMID: 10363620

3. Anderson P, Cochran B. Personal experiences with the clinical use of intravenous therapies. AMSA, BIORC and Private clinic data. Seattle Washington,2014

4. Ferry D R, Smith A, Malkhandi J, et al. Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for in vivo tyrosine kinase inhibition. Clin Cancer Res 1996;2:659-668.

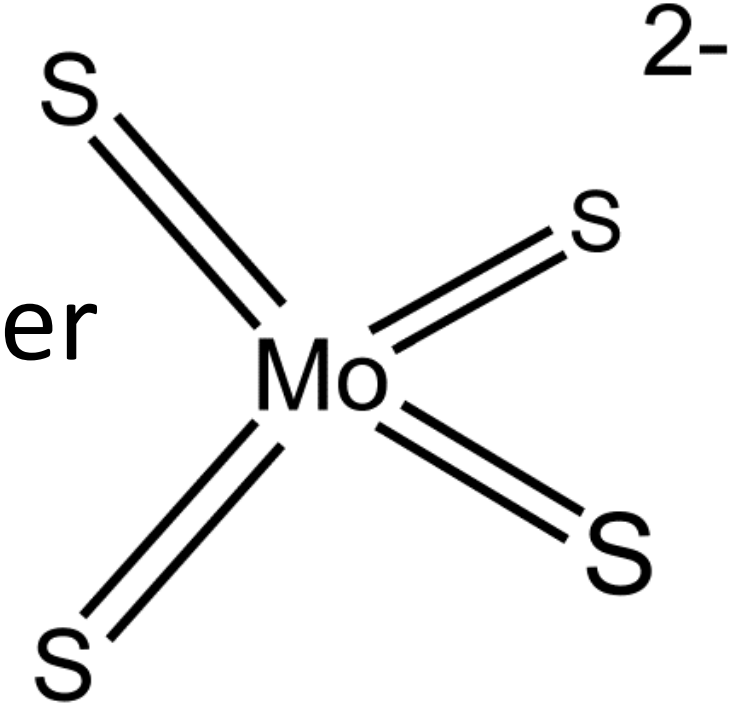
5. Zhi-ping Yuan, Li-juan Chen, Lin-yu Fan, et al. Liposomal Quercetin Efficiently Suppresses Growth of Solid Tumors in Murine Models. Clin Cancer Res 2006;12:3193-3199.

Angiostatic treatments: Copper chelation using TM.



Tetrathiomolybdate (TM)

- Effective oral copper chelator
- Used for Wilson's Disease
- Currently investigation for cancer



Copper

- Liver is the major storage site
- Carried on albumin to the liver
- Binds to apoceruloplasmin to form **ceruloplasmin** in the liver

Copper Functions

- Energy production (cytochrome c)
- Connective tissue formation (lysyl oxidase)
- Iron metabolism (ferroxidase I)
- CNS (Dopamine-beta-monooxygenase)
    - Dopamine → NE
- Melanin formation (tyrosinase)
- Antioxidant function (SOD)
- Gene expression

High Copper Foods

- Calf liver (15mg)
- Beef (15 mg)
- Veal (12 mg)
- Lamb (10 mg)
- Mollusks
- Clams
- Goose
- Lobster
- Salmon
- Crab
- Anchovy
- Cod
- Squid
- Whole milk
- Garbanzo beans/Lentils/Red/Lima Beans
- Nuts/Seeds
- Amaranth/Barley/Buckwheat/Quinoa/Rye/Spelt
- Collard greens
- Avocado
- Seaweed (spirulina)
- Mushrooms
- Soy flour
- Pumpkin
- Sweet Potato
- Cocoa/chocolate
- Apricots/Coconut/Figs/Prunes/Raisins

Source: Nutritiondata.com and Food Pharmacy

Tetrathiomolybdate (TM)

So why use it with cancer?

Tetrathiomolybdate (TM)

- Inhibits angiogenesis by lowering (VEGF, FGF2, IL-6, and IL-8)[1]
- Inhibits NFκB[2]
- Enhances radiotherapy[3]
- Enhances chemotherapy[4,5,6]

Human trials

Phase I Trial: Melanoma, angiosarcoma, nasopharyngeal, kidney, breast, colon, lung, pancreas.[7]

- **6 of 18** achieved target copper depletion(Ceruloplasmin 5-15 mg/dL)
- **5 of 6** had no tumor growth or new tumors for greater than 4 months (duration of study)

Human trials

Phase II Trial: Advanced kidney cancer.[8]

- **15 of 15** achieved target copper depletion(Ceruloplasmin 5-15 mg/dL)
- **4 of 13** had no tumor growth or new tumors for greater than 6 months (duration of study)

Human trials

Phase II Trial: Mesothelioma.[9]

- **30 of 30** achieved target copper depletion post surgery (Ceruloplasmin 5-15 mg/dL)
- Non-TM patients showed progression in 20 months. TM patients showed progression at 20 months.

Human trials

Phase II Trial: Castration-resistant prostate cancer.[10]

- **17 of 19** achieved target copper depletion (Ceruloplasmin 5-15 mg/dL)
- No delay of diease

Human trials

Phase II Trial: Breast cancer (28 stage 2/3, 12 stage 4) Some stage 2 NNN. All no evidence of disease.[11]

- **30 of 40** achieved copper depletion (Ceruloplasmin <17 mg/dL)
- **24 of 30 (85%)** relapse-free in 10 months
  - 91% relapse free in NNN breast cancer

A phase II study of copper-depletion using tetrathiomolybdate (TM) in patients (pts) with breast cancer (BC) at high risk for recurrence: Journal of Clinical Oncology; 2017

Sheena Sahota, Naomi Kornhauser, Amy Willis, Maureen M. Ward, Tessa Cigler, Anne Moore,

- **Background:** The tumor microenvironment (TME) plays a critical role in the spread of tumors. Bone marrow derived VEGFR2^{+}endothelial progenitor cells (EPCs) and copper-dependent lysyl oxidase (LOX) are key in tumor progression. We hypothesized TM-associated copper depletion inhibits tumor metastases by reducing the number of EPCs and other copper dependent (CD) processes in the pre-metastatic niche. These results are an update with longer follow-up. **Methods:** Phase II study of BC pts at high risk for recurrence, defined as node+ triple negative (TNBC), stage 3 and 4 with no evidence of disease (NED) were enrolled on a trial of CD with TM. Ceruloplasmin (Cp) levels were maintained between 8-16 mg/dl for two years with an extension phase or until relapse. The primary endpoint was change in EPCs measured by flow cytometry before and during treatment. Secondary endpoints included tolerability, safety, PFS and LOXL-2 levels. **Results:** 75 pts received 2650 cycles of TM on primary and extension study. The median age is 51 years (range 29-66). Forty-five pts have stage 2/3 BC and 30 with stage 4 NED. TNBC pts were 48% and 40% of pts are stage 4 NED. Median Cp level decreased from 28 to 16 ($p < 0.0001$) after one cycle. Copper depletion was most efficient in TNBC where Cp levels dropped from 23.5 to 13 after one cycle. TM was well tolerated with grade 3/4 toxicities including: reversible neutropenia (2.3%), febrile neutropenia (0.04%), fatigue (0.2%). Five-year analysis showed a decrease in EPC's ($p = 0.004$) and LOXL-2 ($p < 0.001$). At a median follow-up of 6.9 years, the EFS for 75 pts is 75.6%. PFS for 36 pts with TNBC is 79.2%. EFS for stage 2/3 TNBC is 90% and for stage IV TNBC is 66.7%. **Conclusions:** TM is safe, well tolerated and appears to affect multiple components of the TME creating an inhospitable environment for tumor progression especially in high risk patients such as TNBC. Randomized trials are warranted, especially in patients at high risk for relapse.

Labs/Work Up

- CBC, CMP, Ceruloplasmin, UA
- Normal ceruloplasmin (20-35 mg/dl)
- Avoid with penicillamine and bone marrow toxic drugs
- **CAUTION WITH CHEMO:** (Reduction of RBC, WBC, etc cell counts)
- Follow up labs every 1-3 weeks.

Warn Patient

- This will be a long term therapy
- Cost is between $150 - $300 per month.
- **If surgery is require allow levels to reach low normal for 6 weeks to ensure adequate angiogenesis for wound healing.**
- **Must have labs drawn at frequency you set up between 1-3 weeks.**
- **CERULOPLASMIN WILL INITIALLY INCREASE!!!**

Side Effects

- **Anemia**
- **Neutropenia**
- Thrombocytopenia
- Leg cramps
- Fatigue
- Dry skin
- Thinning hair
- Nausea
- Burping rotten egg taste after taking cap

Goal of Treatment

- **<u>Ceruloplamsin between 5-15 mg/dL (10-15 mg/dL tolerated best)</u>** or as low as possible **without** serious anemia/neutropenia
- Decreased tumor markers, tumor size or stability.
- May work longest with individuals to hold in remission.

Treatment

- Low copper diet
- Purified water
- No copper cookware or utensils
- Avoid copper supplements
- Consider copper depletion support with Zinc citrate, NAC, and/or ALA.

Treatment

- TM dosed initially at 20 mg p.o. TID cc and 60 mg hs empty stomach for 1-2 weeks. (See how patient tolerates therapy)

<u>Then….</u>

- TM dosed 40 mg p.o. TID cc and 60 mg hs empty stomach. (180 mg qd)
- *Takes about **30-60 days** to reach ceruloplamin goal*

Treatment

- Once goal of 5-15 mg/dL is reached.
- TM is taken 40 mg cc TID and 20 mg hs empty stomach. (100 mg per day)
- Then can eventually go to 20 mg TID or lower. Titrate based on patient.
- Use other copper chelation supplements to lower TM.

Other copper chelators

Zinc + NAC can help maintain ceruloplasmin so patient can take less to possibly no TM.

- Zinc citrate: 150 – 300 mg per day with food
- NAC (N-acetyl-cysteine): 2-4 gram/day. Start with low and work up. (Hydration important with this)
- R- ALA (Alpha lipoic acid): 100-400 mg/day (Best empty stomach)

Other considerations

- If ceruloplasmin comes down slow or not at all, despite doses of TM up to 200 mg/day.
    - There is increased hepatic need for sulfur compounds:
    - Consider: NAC, ALA, Taurine or MSM

Other considerations

- Low glucose conditions enhance TM[12]
- Consider low glycemic or modified ketogenic diet.

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