'All truth passes through three stages: First, it is ridiculed; second, it is violently opposed; and third, it is accepted as self-evident.'
Arthur Schopenhauer (1788-1860)

A CLINICAL TRIAL OF ONE

Discussion of an ovarian cancer patient's therapy

Important - Disclaimer

- IMPORTANT: This protocol is experimental and was designed for a specific patient. There is no guarantee that the ideas contained within this document will yield improved cancer treatment outcomes – and they should never be attempted without the supervision of a knowledgeable physician – preferably an oncologist. It is possible that the ideas proposed in this document might result in physical harm, poor cancer outcomes and/or death. The author assumes no responsibility for adverse events resulting from attempts to utilize the ideas and theories contained within this document.

My Background

- Currently work as an Inpatient Pharmacist at a hospital that treats many cancer patients
- Graduated from the University of Colorado School of Pharmacy in 2001(BSPharm, Magna Cum Laude)
- Pharmaceutical Sciences PhD coursework completed through preliminary exams (research interest - accelerated testing of proteins and peptides)
- Two rotations away from completing my non-traditional PharmD
- I changed from a career involving engineering and problem solving when I became a Pharmacist
- I am NOT a chemotherapy Pharmacist

Case Background Information

- Diagnosis of Stage IV Ovarian Cancer – April 2009
- Verified by biopsy
- Neoadjuvant chemotherapy
  - 8 cycles intravenous chemotherapy
  - Surgery after 4th cycle
- Two different types of cancers (ovarian and tubal) were found at post surgery biopsy
- Now believed to be in remission
  - Approximately 12 months post last chemo cycle

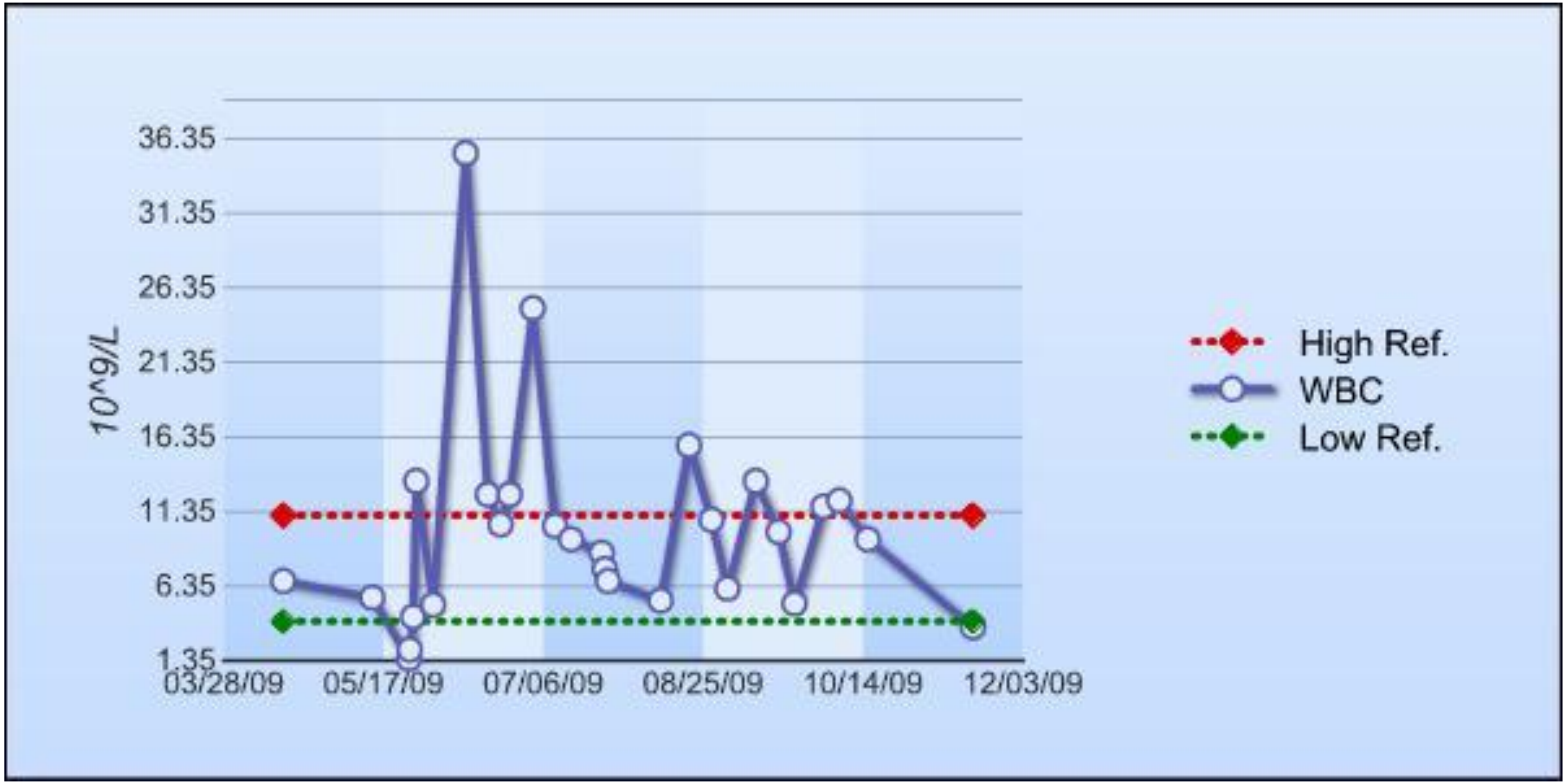
Diagnosis – April 2009

- You don't look right. See if you can get in to see the doctor tomorrow.
- Honey, they found something, and I'm not supposed to leave till they tell me to.
- They just want you to see a specialist because masses this big can be cancerous. It's probably nothing.
- What do you mean I can't get in to see the doctor till …?
- Who is this Doc? Does he know what he's doing? How good is he?
- April 15th, 2009 – you have Stage IV Ovarian Cancer.
- Let's biopsy it to double check, but there isn't any doubt in my mind…
- Would you be willing to donate tissue to a study… ?
- Sign here to agree that you give up all commercial claims against the company that gets the tissue.
- Should we go to MD Anderson?
- No, we'll stay here – for now. I don't want to be away from home.

Chemotherapy Toxicities

- Peripheral Neuropathy
- Extreme Pain (organs, bones)
- Neutropenia
- Hearing Loss
- Lung Damage
- Chemo Brain
- Clotting problems
- Loss of Taste
- Impairment of Smell
- Hair Loss
- Extreme Fatigue
- Nausea
- Renal Impairment
- Etc…

Chemotherapy Toxicities (continued)



Chemotherapy Toxicities (continued)

Realities

- Regardless of therapy – and if they survive the therapies - Stage III and Stage IV Ovarian Cancer patients have very poor survival rates
- Obviously, we don't know what we're doing relative to treating this disease
- Patients know these facts - so, they blindly add supplements and other things to their regimens to construct 'Clinical Trials of One' that are based on myths, rumors and legends

Conclusions and Beliefs

- Cancer doesn't kill you
  - **Too much** cancer kills you
  - Cancer at the **wrong place** kills you
- Current treatment strategies can't kill all the cancer cells
  - Extremely adaptable
  - Highly heterogeneous cell populations
- What's left are the nastiest and the meanest, and you will not be able to control them
  - No competition
  - Progress without restraint of tumor 'system'
  - Real world results and numerous computer models support these theories

Bottom Line

- The current state of therapy for advanced Ovarian Cancer was highly unlikely to save my wife's life
- It was improbable that a breakthrough would occur that would fundamentally change that conclusion
- The only choice was to apply engineering thinking and pharmacist knowledge to the task of trying to formulate an alternative evidence based regimen
- A 'Clinical Trial of One'

Proposal of a Clinical Trial of One

- An evidence based attempt to achieve cancer cell stasis via synergistic modulation of multiple cellular pathways (e.g. COX2, NF-κB, mevalonate, estrogen, and GADD45α & GADD45γ) utilizing medications that are readily available, and whose side effect profiles and toxicities are usually relatively benign, well understood and commonly managed.

Objective

- Extension of remission time for a Stage IV Ovarian Cancer patient via blockage of and/or retardation of the reproduction of cancer cells that survived and/or were generated by the chemotherapy series used to achieve remission.

Strategy

- This regimen will attempt to utilize currently available medications to safely impact cellular pathways that uniquely drive or enable the progression of cancer cells, with one set of pathways being unique to many gynecological and breast cancers.

Clinical History

- CM is a 55 year old female who has completed 8 chemo cycles of a neoadjuvant treatment plan for Stage IV ovarian cancer, and who is now in remission. The chemotherapy agents used were carboplatin and docetaxel. Surgery occurred post cycle 4 and resulted in the removal of all visible tumor mass. At diagnosis, biopsy showed a tumor that expressed CK7, CK20, and WT1 and was negative for P16. Post surgery biopsy revealed tumor masses on both ovaries that appear to have been platinum/taxol sensitive – with those tumors being largely necrotic. A second tumor type of approximately one centimeter was found on one of the fallopian tubes, and this tumor appeared to be resistant to the chemo regimen as it was found to be 100% viable. The phenotype of this tumor has not been characterized.

Clinical History Addendum

- Subsequent testing of both tumor types relative to estrogen and progesterone receptor expression yielded the following:
  - Ovarian tumor tissue expressed functional estrogen receptors and exhibited greatly reduced progesterone receptor function and expression.
  - Tubal tumor tissue expressed estrogen and progesterone receptors normally.
  - The two tumor types were believed to be unrelated to each other.

Regimen Basics

- Some substances administered daily
  - 325mg aspirin twice a day (COX enzyme pathways)
  - Femara™ (letrozole) (aromatase inhibitor – estrogen pathways)
- Some substances administered for 3 weeks every 3 months
  - Salsalate (high dose – saturated metabolism & protein binding - NF-κB & GADD45α & GADD45γ pathways)
  - Lipitor™ (atorvastatin – mevalonate, JNK pathways?)

Regimen Overview

Pulse Phase Medications

Targeted Pathway	Therapeutic Class	Agent	Target Dose	Frequency
NF-κB	NSAID	**Salsalate**	**1500 mG**	**Twice a Day**
Mevalonate	Statin	**Lipitor® (atorvastatin)**	**80 mG**	**Daily**
GADD45α & GADD45γ	Will rely on salicylate from the salsalate dose to impact this pathway. If cancer appears to be reoccurring it is recommend that either diclofenac or sulindac be added to the regimen to more aggressively impact this pathway. Finasteride is a non-NSAID option that should be seriously considered if diclofenac or sulindac are contemplated. Finasteride would make an aromatase inhibitor mandatory.			

Continuous Medications

Targeted Pathway	Therapeutic Class	Agent	Dose	Frequency
COX2	NSAID	**Aspirin**	**325 mG**	**Twice a Day**
Estrogen	**Aromatase Inhibitor**	**Physician's Choice**		

Supporting Rationale

- Aspirin (325mg BID)
  - COX-2 seems to be associated with tumor metastasis
    - Inflammation drives metastasis mechanisms and tumor progression
  - Aspirin may also act as an aromatase inhibitor through down regulation of prostaglandin pathways
  - Numerous studies and journal articles that show significant risk and mortality reductions for multiple cancers are now coming to the public's attention
    - Breast Cancer (initial incidence and progression if non-metastatic), Hodgkins, Colon, Prostate, Esophageal

Supporting Rationale

- Salsalate
  - Aspirin and NSAIDs are capable of inducing cancer cell apoptosis & cell death, and retarding tumor growth and progression
    - NF-κB and associated pathways
    - GADD45α & GADD45γ pathways
    - Other pathways (e.g. ibuprofen impacts PPAR)
  - Concerns about safely achieving adequate plasma concentrations
  - Salsalate and Aspirin are unique
    - Saturable metabolism and protein binding

Supporting Rationale

- Salsalate (continued)
  - Demonstrated ability to down regulate human NF-κB and associated pathways at historically 'safe' and physiologically achievable plasma concentrations
    - Reversal of Type 2 diabetes
      - Elimination of crosstalk between inflammation pathways and insulin receptors
      - Type 2 diabetes always reoccurs when high dose salicylate is reduced or stopped

Supporting Rationale

- Statins (hydrophobic)
  - Evidence that indicates aspirin, NSAIDs and COX2 Inhibitors may work synergistically with statins to halve the concentrations required by both drug families to induce cancer cell apoptosis
    - JNK, Mevalonate Pathways?
    - Unknown mechanism(s)
    - Effect clearly demonstrated in a study that looked at lovastatin and Celebrex™ co-administration effects (in vitro study)
  - Conflicting evidence relative to statins effectiveness against cancer cells
  - Serious concerns about safety at adequate plasma concentrations

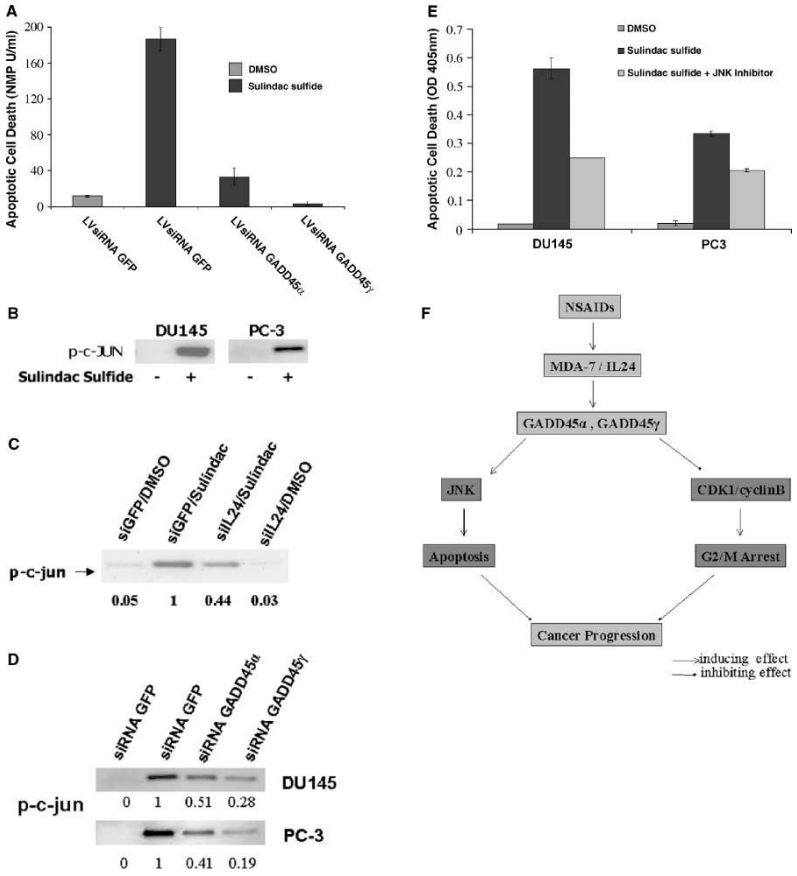
Supporting Rationale

- Aromatase Inhibitor
  - Estrogen receptors are reported to drive the growth and progression of many ovarian cancer tumors. In fact, it is reported that > 90% of confirmed ovarian cancers have lost their progesterone receptors' function. This allows unopposed estrogen receptor stimulation of the tumor's cells, and it has been reported that > 80% have retained their estrogen receptors' functionality.

Supporting Rationale

- Aromatase Inhibitor
  - If finasteride is added to the regimen to impact GADD45α & GADD45γ pathways an aromatase inhibitor is mandatory if patient has estrogen receptor positive cancer cells
    - Finasteride drives testosterone pathways to produce more estrogen
    - MUST be careful - these pathways are associated with cell REPAIR when cell is under stress

Supporting Rationale - Finasteride



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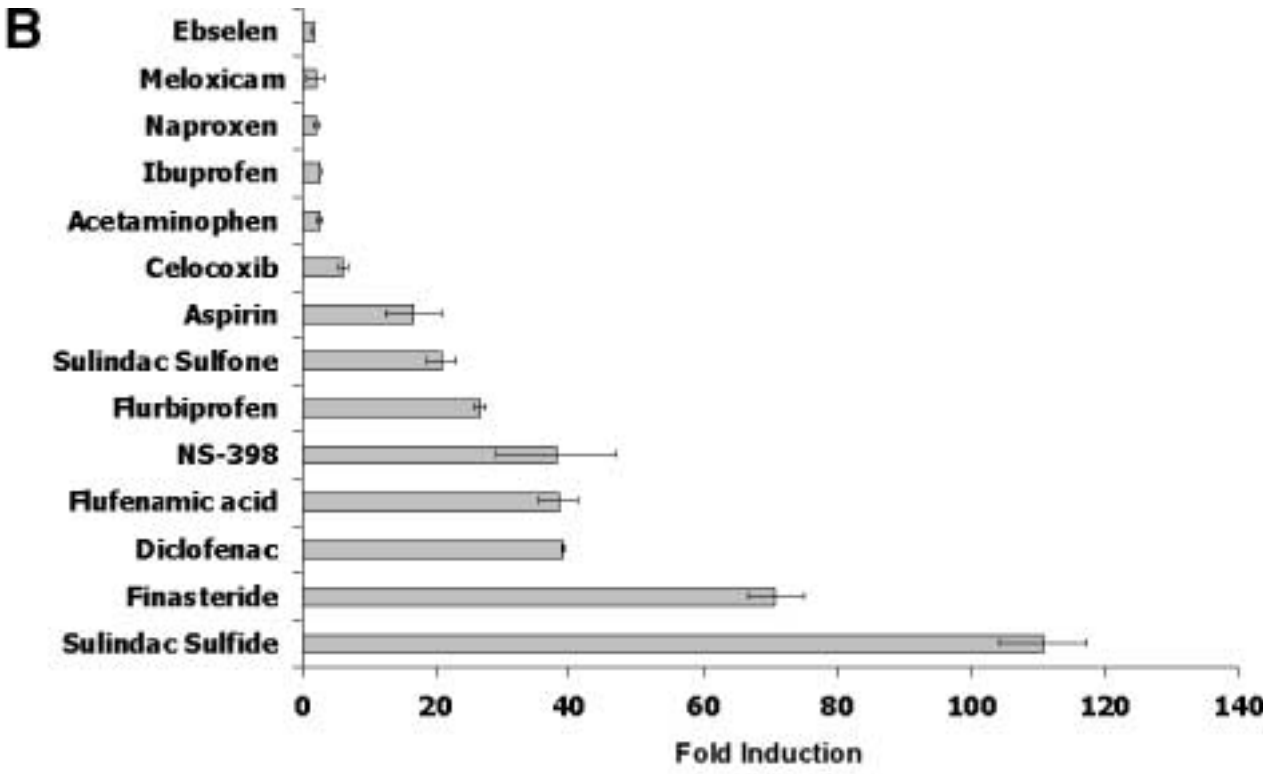
Supporting Rationale - Finasteride



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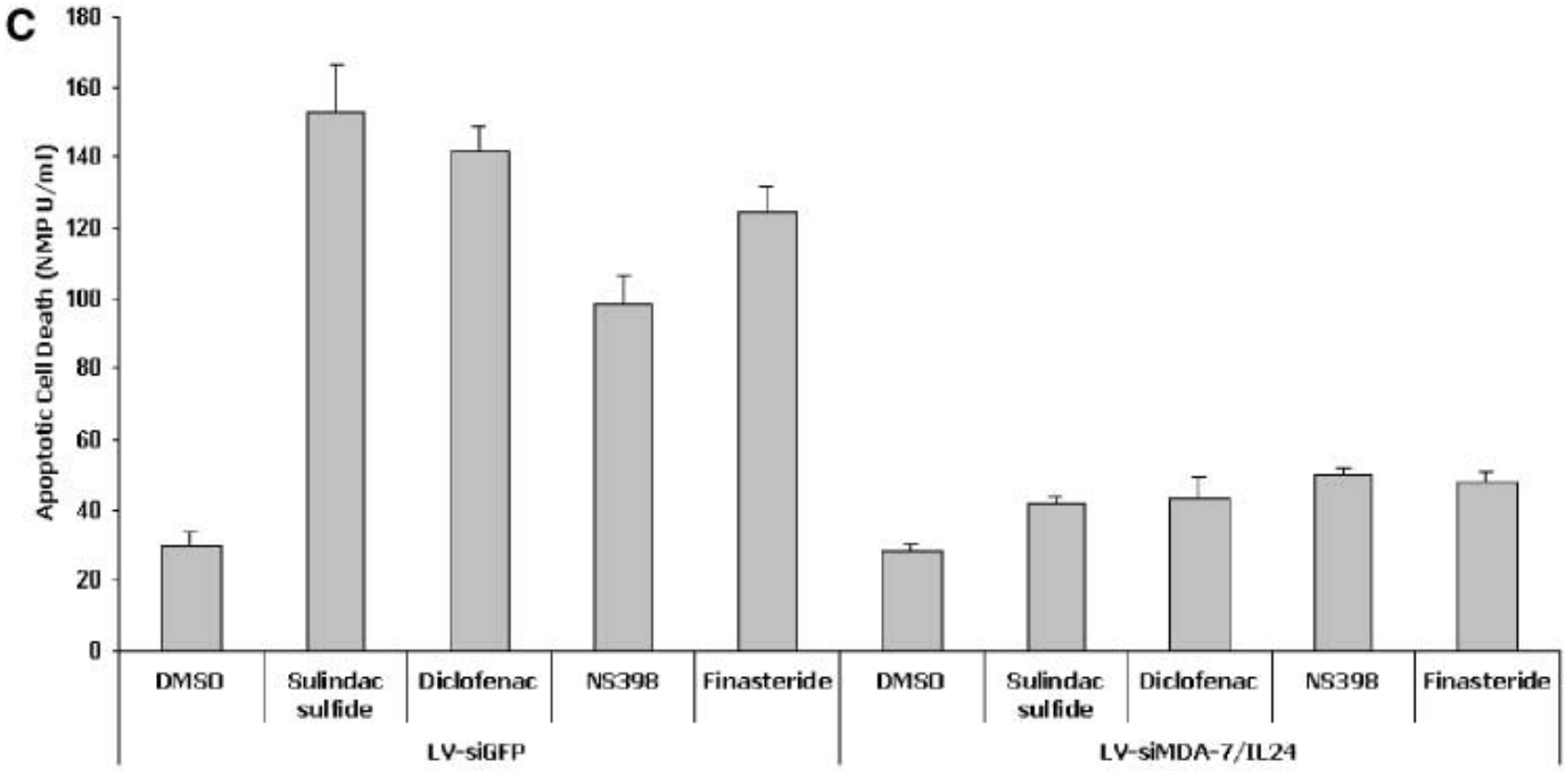

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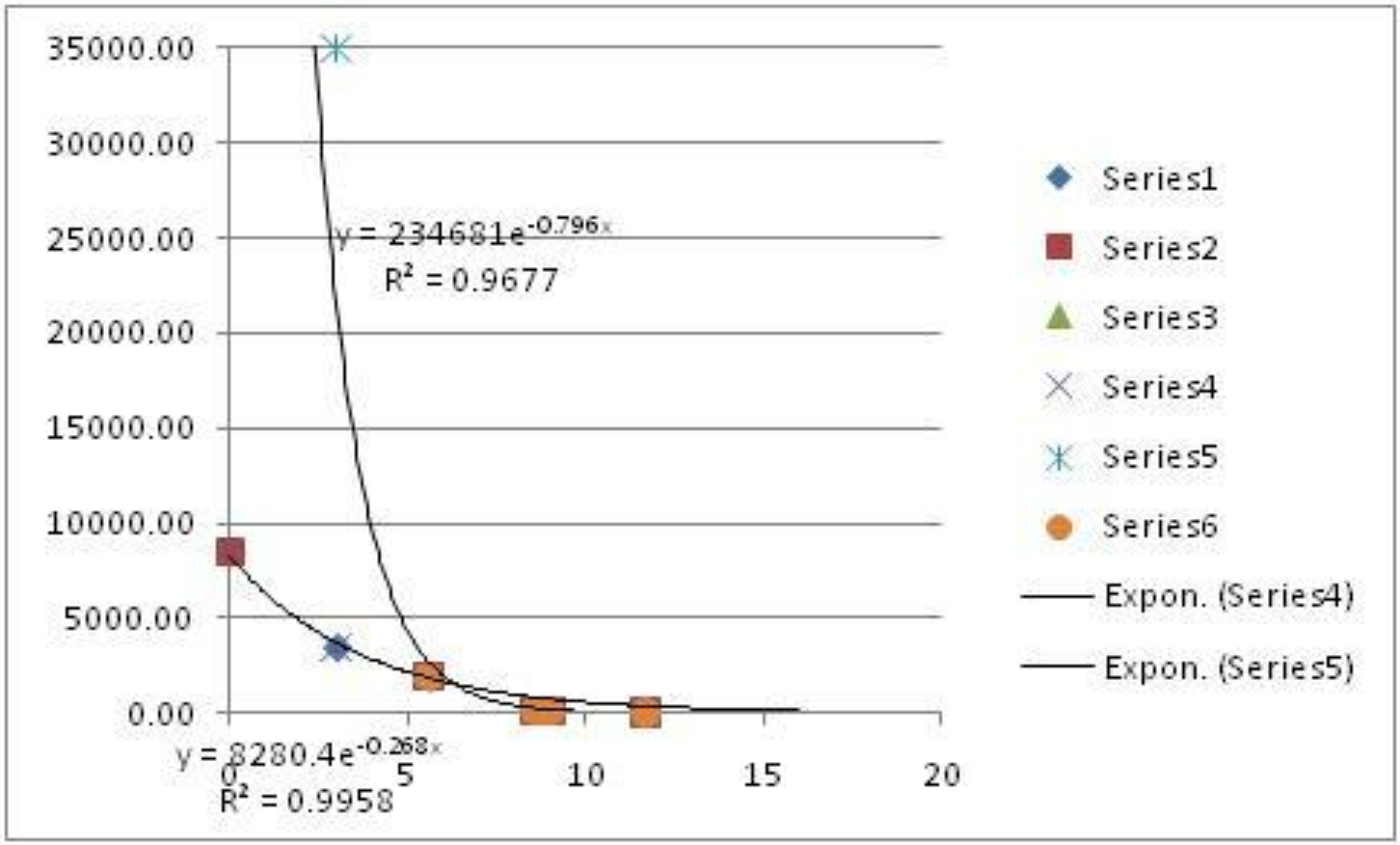
Supporting Rationale - Finasteride

- Very Large Therapeutic Window
- Calculations Indicate Achieving Therapeutic Plasma Concentrations Probable

CA125 Plots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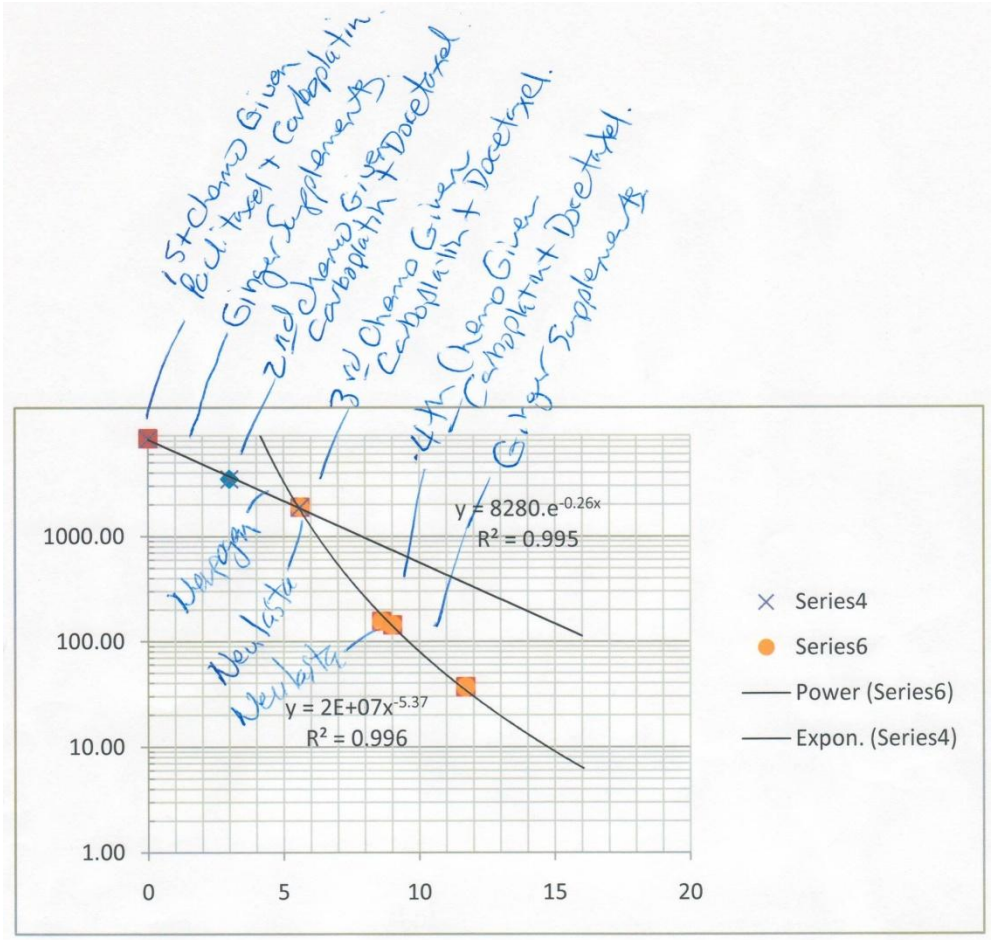
y = 234681e-0.796x
R² = 0.9677
y = 8280.4e-0.268x
R² = 0.9958
Series1
Series2
Series3
Series4
Series5
Series6
Expon. (Series4)
Expon. (Series5)

CA125 Plot vs Events



What Changed??????

- Started High Dose Ginger Supplement
  - Immediate and Profound Relief of Chemo Associated Side Effects Were Observed
    - Anti-Inflammatory substances and mechanisms?
    - Unknown mechanism(s)
- Started Neulasta™
  - Stimulation of G-CSF Receptors and Associated Increase In Tumor Kill Ratio?
    - Approximately 50% of Ovarian Cancer tumors express G-CSF receptors
    - Does Neulasta™ cause a stimulation that causes an increased number of cells to be killed?
- Stopped Taking Singulair™
  - Immune System Effects?

Ginger Supplement

- E-mail To Patient From a Friend – 'Hey, Check This Link - Ginger Kills Ovarian Cancer'
  - Ginger Raises New Hope In Fight Against Ovarian Cancer http://www.guardian.co.uk/uk/2006/apr/18/science.health
  - Ginger Causes Ovarian Cancer Cells To Die, U-M Researchers Find http://www.med.umich.edu/opm/newspage/2006/ginger.htm
  - Ginger Inhibits Ovarian Cancer Cell Growth http://chinesemedicinenews.com/2008/01/02/ginger-inhibits-overian-cancer-cell-growth/
- The Studies –
  - J. Rhode, S. Fogoros, S. Zick, H. Wahl. K. A. Griffith, J. Huang, J. R. Liu 2007. **Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells.** *BMC Complementary and Alternative Medicine* 7: 44-53.
  - B. H. Ali, G. Blunden, M. O. Tanira, A. Nemmar 2008. **Some phytochemical, pharmacological, and toxicological properties of ginger (*Zingiber officinale* Roscoe): A review of recent research.** *Food and Chemical Toxicology* 46: 409-420.
- The Story and the Recipe
  - Can Ginger Cure or Slow Down Ovarian and Other Cancers? http://thatcrazypharmacist.com/?p=42
  - Recipe for 'Catherine's Potent Ginger Concoction' http://thatcrazypharmacist.com/?p=87

Considered Explanations

- CA125 is an Unreliable Marker of 'System' Response
- Tumor Collapse
- Various Kinetic Models of Tumor Death
  - Note: The radiology folk are the guys to read for this topic
- Lab Data Entry Error
  - Repeated enquiries to lab across ALL shifts and multiple levels of personnel has always yielded negative on this one
- Change in measurement system range/resolution
- Change in measurement system

Add On Measures

- Nutrition
  - Avoidance of Inflammation Producing Substances
  - Avoidance of Various Cooking Oils
  - Avoidance of Various Fats
  - More Vegetarian Eating Patterns
  - Quercetin (juiced whole apples, onions, etc)
  - Curcumin (Tumeric Oil Blend)
- Supplements
  - Capsule Multivitamin/Multimineral without Iron
  - Selenium 200mcg
  - Niacinamide 500mg
  - Iodine and Potassium Iodide 12.5mg/day (Lugol's Solution 2%)
  - Vitamin C (from daily juice and ginger drink)
  - Vitamin D 2000 IU
  - High Lignin Flax Seed Oil/Hemp Seed Oil Blend Modeled
  - CoEnzyme Q10 (ubiquinone) 100mg/day
  - Black Elderberry Elder Flower Extract

Environmental

- Avoidance of Estrogenic Compounds
- Avoidance of Fluoride
- Avoidance of Brominated Flour Products

Interactions With Providers

- Polite and professional tolerance of crazy pharmacist husband
- Growing credibility across time
- Critical review of evidence based 'clinical trial of one' proposal
- Interest and Agreement to help
- 'Nice job'
- Ongoing observation
- What I consider 'Teamwork'

What Next?

- Continue looking for ‘convergences’
  - Eclectic Physicians
  - Thompsonian Physicians
  - Allopathic Physicians
  - Herbalist Knowledge
  - Native American Knowledge
  - Ancient Healers
  - Chinese Medicine
  - Integrative Oncology
  - Current Science Knowledge
- Pray