

PERSONALIZED TREATMENT OPTIONS REPORT

PREPARED ESPECIALLY FOR
XXXXX XXXXXX

PREPARED BY
MOSHE ROGOSNITZKY
ADJUVANT MEDICAL SOLUTIONS
WWW.ADJUVANTMED.COM

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INTRODUCTION

Mrs. Xxxxx Xxxxxx (born Aug 6th, 1973) was diagnosed with invasive breast cancer in February 2006. A bilateral mastectomy was performed as well as a bilateral oophorectomy. There has been gradual progression of disease including metastasis to the liver, to the lung and the brain despite numerous therapies.

Due to the continued progression of disease and exhaustion of almost all standard therapies, Mrs. Xxxxxx has chosen to explore additional approaches to treating her disease. Part of this process has involved the performing of extensive gene expression analysis on blood samples, as well as neurotransmitter and neuropeptide analysis. The purpose of these tests is to shed light on the environment within which the disease exists and progresses, and to identify targets for manipulation in the hope that this will lead to a slowing down or reversal of the disease process.

What follows is an overview of the clinical and laboratory findings and a selection of those options deemed to be most appropriate in this situation together with the rationale for each. These are chosen primarily for their favorable risk-benefit ratio as well as their ability to simultaneously target multiple abnormalities identified. Modifications should be made based on ability to comply with regimen and response. Any decision on implementation of all or part of the options below should be made by Mrs. Xxxxxx's physicians.

DIAGNOSTIC OVERVIEW

HISTORICAL FINDINGS

Mrs. Xxxxx Xxxxxx (born Aug 6th, 1973) was diagnosed with invasive breast cancer (triple negative) in February 2006. She carries the BRCA1 mutation. A bilateral mastectomy was performed as well as a bilateral oophorectomy. There has been gradual progression of disease including metastasis to the liver , lung and brain despite multiple therapies including CEF + Taxotere, radiation, Xeloda + Avastin, Gemcitabine + Avastin + Zometa, Navelbine + Avastin, Ixempra + Avastin.

Height 5'5", Weight 155lbs (stable), Blood Pressure 110/90

LABORATORY FINDINGS

General

Results in black = positive findings

Results in red = negative findings

↑ Homocysteine 9.21 umol/L

↑ CA27.29 66.06

EBNA IgG – Positive

EBV early Ag antibodies – Positive

Thyroglobulin Antibodies – Positive

TSH 5.38

Ferritin 101

Cytokines & Growth Factors

↑ p53 Protein Level

↑↑ p53 Gene Expression

↑↑ BAX Gene Expression

↑↑ p21 Gene Expression

↑ IL-5 Gene Expression

↑↑ IL-12 Gene Expression

↑↑ IFN- γ

↑↑ TNF- β Gene Expression

↑↑ TRAIL Gene Expression

↓ FGF-B Gene Expression

↑↑ p185 (HER-2) Soluble Level

↑ EGFr Soluble Level

↓ BCL-2 Gene Expression

↓ IL-2 Gene Expression
↓ IFN- α (non-reactive level)
↑↑ TGF- β1 Gene Expression
↓ Dextrorotatory Lactic Acid Level
↑↑ Survivin Gene Expression
↑↑ TM-2PK Gene Expression
↑↑ IL-4 Gene Expression
↑↑ IL-6 Gene Expression
↑ IL-8 Gene Expression
↑↑ IL-10 Gene Expression
↓↓ CD10 (Neprilysin) Gene Expression
↑↑ PDGF-R β Gene Expression
↑↑ VEGF Gene Expression
↑↑ FAS-Ligand Gene Expression
↑↑ Non-Genomic DNA + RNA Levels
↑ P-Glycoprotein Level
↑ MDR-Associated Proteins
↓ Adrenaline and Adrenaline Metabolites

Neurotransmitters and Neuropeptides (urine)

Adrenaline- Trace
Noradrenaline – trace
Dopamine 100%
5-HT – Trace
GABA – Trace
Acetylcholine – Trace

Neurotransmitter Precursors

DOPA – Abent
Phenylalanine – Absent
Tyrosine – Elevated
5-HTP – Absent
Tryptophan – Absent

Neurotoxins and False Neurotransmitters

Epinine – High
Phtalates – Low
THP – low

Neuropeptides

↑ Vasopressin
↑↑ Met-Enkephalin

SUMMARY OF FINDINGS

The p53 gene expression is very high and whilst this is a positive finding it should result in similarly elevated levels of p53 protein. The p53 protein level is not as elevated as would be expected. This could be a result of some mutation of p53. The p21 gene expression is very high. This usually happens when p53 is not sufficiently active. Pro-apoptotic BAX is very high and anti-apoptotic BCL-2 almost non-detectable. The pro-apoptotic system appears capable but is being inhibited by other mechanisms.

Resistance to apoptosis is signified by the elevations in Multi-Drug-Resistance- associated proteins as well as P-Glycoprotein. This is one aspect of mechanisms of resistance to apoptosis-inducing drugs and a strategy to suppress MDR proteins could be beneficial.

Additional resistance is signified by the high level of survivin – an anti-apoptotic protein produced by cancerous cells. Using survivin-suppressing agents could be beneficial. Until resistance to apoptosis is overcome it would be advisable to preferentially pursue necrosis-inducing therapies.

There is hyper-glycolysis signified by the elevated TM-2PK and this is probably responsible for the rapid growth rate of the tumor. Correcting abnormal glycolysis should be a priority.

Tumor growth is stimulated by elevations of IL-10, low levels of CD10, elevated VEGF, elevated PDGF and elevated PDGF Receptor Beta. The elevation of PDGF-R β signifies that cells are hyper sensitive to stimulation by the ligand (PDGF) which is over-expressed. Therapies targeted at PDGF-R β could be beneficial. It should be noted that Gleevec as a monotherapy has not been shown to have any effect^{1,2} in advanced breast cancer and this agent should probably be avoided. There may be some PDGF-R β antagonists in clinical trials. A few natural agents have been demonstrated to inhibit PDGF-R β . In addition to targeting PDGF-R β every effort should be made to inhibit PDGF release from platelets by appropriate agents.

Underlying inflammation is signified by elevations of PDGF and IL-6.

MMP-2 and MMP-9 levels are reasonably normal and this could be a beneficial result of the MMP inhibiting effects of Doxycycline.

HER-2 (soluble receptor) levels in serum are significantly elevated and this has been correlated with elevated HER-2 expression in tumors^{3,4}. Whilst HER-2 status of the primary tumor was originally negative, discordance is sometimes found between HER-2 status in metastatic and primary tumors⁵. It may be useful to check for HER-2 expression in metastatic lesions. At the same time it should be considered that due to the high soluble HER-2 level, Herceptin will be preferentially bound by it and inactivated. It is possible that a higher dose would compensate for this effect however this assumption is hypothetical.

A suppressive growth factor - OGF (met-enkephalin) is elevated in urine. However, CD10 which cleaves OGF is very low. This could be indicative of either an increased requirement for OGF or more likely a deficiency of OGF receptors, or both. Correcting this abnormality is essential and may require increasing production of receptors in addition to replenishment of the ligand.

Dopamine levels account for 100% of neurotransmitters found in the urine. Whilst dopamine has tumor-suppressive properties, at levels as high as this it over-stimulates certain immune reactions which lead to autoimmunity and production of auto-antibodies. Autoimmunity is signified by the extreme elevations of IL-10⁶ and TGF- β . TGF- β has also been shown to be a driving factor in progression of triple negative breast cancer⁷.

Dopamine dominance also suppresses thyroid function⁸⁻¹⁰. It may be beneficial to correct this by administering a low dose of Cytomel (Liothyronine sodium) – which has also been reported to have anti-tumor effects in advanced breast cancer¹¹. This could also help deal with the adrenaline dysfunction present as demonstrated by lack of any urinary adrenaline or metabolites.

In a normal situation dopamine is converted by dopamine- β -hydroxylase to noradrenaline. In turn noradrenaline is converted to adrenaline. Dopamine β -hydroxylase is a copper and oxidation dependent enzyme. The suppression of this enzyme is likely linked to low copper levels as well as inhibition of oxidation. As Mrs. Xxxxx is consuming numerous and high doses of antioxidants – it may be advisable to reduce these at least temporarily.

Extremely high levels of non-genomic DNA + RNA point to a strong viral process. This may either be the direct cause of the cancer growth; the indirect cause through activation of growth and immune-dysregulating factors; and/or interference with neurotransmitter activity. Substantial evidence exists of the involvement of HPV, MMTV and EBV in breast cancer¹². EBV does seem to be active as shown in recent blood tests. It may be necessary to target virus/es which could be in both active and latent phases. Interferon-alpha expression is too low for anti-viral effect.

It may be useful to attempt to determine whether the tumor is EBV related through more extensive pathological analysis. There is a relatively non-toxic protocol developed at Dana-Farber Cancer Institute to treat EBV related malignancies. This protocol, comprising arginine butyrate designed to activate the EBV (which is usually in latent state) followed by ganciclovir has resulted in complete remissions in a high percentage of treatment-resistant malignancies¹³⁻¹⁷.

Another agent which is sometimes effective against EBV in its latent phase is cimetidine^{18,19} (or ranitidine). It is also known for its anti-cancer effects. However Mrs. Xxxxx has been taking this at a high dose for quite a while without apparent effect. My concern in using this agent is that long term administration leads to hyper-prolactinemia which may encourage tumor growth.

Elevated urinary tyrosine levels are indicative of sub-optimal liver function.

IN SUMMARY:

- Pro-apoptotic genes are functional but resistance is caused by elevated survivin, PDGF-R β , and Multi Drug Resistance (MDR) proteins.
- Abnormal glycolysis is dominant and a driving factor of rapid tumor growth.
- Angiogenesis is very active despite Avastin. This could be caused by hypoxia aggravated by adrenaline dysfunction.
- Autoimmunity is present and this increases resistance of cells to therapy.
- Presence of a dominant viral process directly or indirectly related to tumor dissemination and neurotransmitter dysfunction.
- A strong inflammatory process is present.
- Dopamine activity is dominant and is contributing to hypothyroidism, adrenal dysfunction and autoimmunity.
- Growth regulating OGF receptor levels are low.
- Liver function is suboptimal.

TREATMENT OPTIONS – INTRODUCTION

It is my opinion that primary focus should be placed on the following strategies:

- Correction of Neurotransmitter function
- Correction of thyroid and adrenaline function
- Anti-viral therapies
- Anti-angiogenic therapies
- Correction of abnormal glycolysis
- Anti-inflammatory therapies
- Correction of the OGF receptor function
- Inhibition of platelet aggregation
- Support of liver and detoxification processes
- Reversal of Multi Drug Resistance

Some of the agents listed below have demonstrated an ability to inhibit tumor growth via known or unknown mechanisms, in addition to their desired molecular effect/s for which they are selected. Whilst it is possible to select only some of the options and implement them in a limited manner, I would suggest that initially it is best to pursue a combination of as many options as are safe, compatible and tolerated. This must obviously be decided by the treating physicians. The listing that follows is NOT in order of importance.

TREATMENT OPTIONS

Item 1

Name: Imiquimod (Aldara) topical application, oral use, or both.

Dose: 2 sachets rubbed on skin twice weekly + 50mg orally twice weekly (with food). Rub on different areas to prevent skin irritation.

Rationale: Induction of OGF-receptor expression²⁰. Induction of interferon-alpha and potent antiviral²¹⁻²³, anti-tumor^{21,24} and anti-angiogenic²⁵ effects. Systemic effects seem to be achieved via topical administration. Oral administration in capsules is possible^{26,27} but at low dose in order to prevent gastric irritation. Preclinical trials examining systemic anti-tumor effects suggest that twice weekly use is as effective as daily use²⁸.

Item 2

Name: Pentoxifylline

Dose: 400mg three times daily.

Rationale: Inhibition of VEGF²⁹⁻³¹, IL-8³²⁻³⁴, IL-4³⁵, IL-6³⁶⁻⁴⁵, IL10^{46,47}.

Item 3

Name: Dipyridamole (Persantin) RETARD

Dose: 200mg once daily (if unavailable in USA, available from UK or Germany). Consider increase to 200mg twice daily after 10 days.

Rationale: Inhibitor of platelet aggregation which is a prime cause of elevated platelet-derived-growth factor. Potent anti-viral effect⁴⁸⁻⁵², anti-cancer effects⁵³⁻⁵⁸, synergistic with Interferon alpha^{59,60} (which is induced by imiquimod). Reduces multi-drug-resistance through multiple mechanisms⁶¹⁻⁶³.

Item 4

Name: Digitoxin (Digitalis)

Dose: to be determined by a physician experienced with its use.

Rationale: Potent anti breast cancer effects⁶⁴⁻⁷¹, inhibition of glycolysis⁶⁸.

Item 5

Name: Interferon Alpha (Roferon) – low dose

Dose: 300,000 units injected subcutaneously every 2nd evening, in early evening hours.

Rationale: Replenishing low interferon alpha levels. Anti-viral effects⁷²⁻⁷⁵, anti tumor effects when used at low doses. This dose is based on the experience of integrative physicians in the USA and UK and is less than 10% of the dose usually used in malignancies. No side effects should be expected with the exception of possible (beneficial) immune reaction at site of injection. Synergistic with dipyrindamole.

Item 7

Name: Green Tea Extracts (EGCG/Polyphenols) (Life Extension Life Extension, Mega Green Tea Extract, Decaffeinated).

Dose: 2 capsules morning and evening with food.

Rationale: Inhibition of PDGF-R β ⁷⁶⁻⁷⁹, VEGF^{80,81}, and numerous other cell-regulating effects⁸¹.

Item 8

Name: Clomipramine

Dose: Start with 10mg twice daily and increase as tolerated. In clinical trial for brain tumors dose was escalated to and maintained at 150mg daily⁸².

Rationale: Acts as a selective mitochondrial inhibitor of cancer cells^{83,84}. May antagonize dopamine⁸⁵. Has been used successfully (off-label) to treat brain tumors in UK for many years. Pre-clinical and clinical research supports this use^{82-84,86-89}.

Item 9

Name: Silibinin Plus® (Life Extension)

Dose: 1 capsule morning and evening with food

Rationale: Liver support⁹⁰⁻⁹⁷, antiproliferative effects.

Item 10

Name: Cynarol® (Flora) – Artichoke Fresh Plant Concentrate

Dose: 2 capsules morning and evening with food

Rationale: Liver & detoxification support. Source of luteolin, a PDGF-R β inhibitor⁹⁸.

Item 11

Name: Selenium (as Sodium Selenite)

Dose: 200 -300mg twice daily

Rationale: Anti-viral effects⁹⁹⁻¹¹⁰.

ADDITIONAL TREATMENT STRATEGIES

The following is a list of strategies that can be employed in order to correct some of the existing abnormalities. Choice of drugs and dosing needs to be decided by the treating physician.

Strategy 1

Correction of brain neurotransmitters pattern, lowering of dopamine, inducing production of serotonin and noradrenaline. The world's most renowned expert in this field, with extensive experience in successfully treating cancer including breast cancer with this approach, is Dr. Fuad Lechin M.D., Ph.D., Chief of the Sections of Neuropharmacology, Neurochemistry and Stress, Institute of Experimental Medicine, Central University of Venezuela. His contact details are at www.lechin.com. He has published a textbook (Neurocircuitry and Neuroautonomic Disorders: Reviews and Therapeutic Strategies, S. Karger Publishers, 2002) detailing how to implement such an approach, with demonstration of its successful results in breast cancer.

Strategy 2

Correction of hypothyroidism and adrenal dysfunction. Several agents are available to achieve this and choice of agents must be decided by a physician with expertise in this field who is able to provide ongoing monitoring.

Strategy 3

Anti-viral treatment. EBV testing in tumor slides can be performed. If it is positive then the protocol from Dana Farber Institute utilizing arginine butyrate followed by ganciclovir¹³⁻¹⁷ could be used. This has to be done under the care of a physician able to implement and monitor such therapy.

MONITORING

FOLLOW-UP TESTS

Certain tests should be repeated at regular intervals in order to monitor the success of the approach/es listed above. The choice of tests can only be determined once the treatment choices have been selected.

REFERENCES

1. Modi S, Seidman AD, Dickler M, et al. A phase II trial of imatinib mesylate monotherapy in patients with metastatic breast cancer. *Breast Cancer Res Treat.* 2005;90(2):157-63.
2. PubMed Snapshot. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18515258?ordinalpos=9&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum [Accessed December 11, 2008].
3. Kong S, Nam B, Lee KS, et al. Predicting tissue HER2 status using serum HER2 levels in patients with metastatic breast cancer. *Clin Chem.* 2006;52(8):1510-5.
4. Witzel I, Thomssen C, Krenkel S, et al. Clinical utility of determination of HER-2/neu and EGFR fragments in serum of patients with metastatic breast cancer. *Int J Biol Markers.* 21(3):131-40.
5. Carney WP, Neumann R, Lipton A, et al. Potential clinical utility of serum HER-2/neu oncoprotein concentrations in patients with breast cancer. *Clin Chem.* 2003;49(10):1579-98.
6. Beebe AM, Cua DJ, de Waal Malefyt R. The role of interleukin-10 in autoimmune disease: systemic lupus erythematosus (SLE) and multiple sclerosis (MS). *Cytokine Growth Factor Rev.* 13(4-5):403-12.
7. Tan A, Alexe G, Reiss M. Transforming growth factor-beta signaling: emerging stem cell target in metastatic breast cancer? *Breast Cancer Res Treat.* 2008. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18841463> [Accessed December 9, 2008].
8. Van den Berghe G, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment. *Crit Care Med.* 1996;24(9):1580-90.
9. Monte O, Zyngier S, Kimura ET, Bianco AC. [Dopaminergic and somatostatinergic pathways decrease serum thyrotropin in rats bearing the 256-Walker mammary carcinoma]. *Arq Bras Endocrinol Metabol.* 2005;49(2):253-64.
10. Strawn JR, Ekhaton NN, D'Souza BB, Geraciotti TD. Pituitary-thyroid state correlates with central dopaminergic and serotonergic activity in healthy humans. *Neuropsychobiology.* 2004;49(2):84-7.
11. GARDNER B, THOMAS AN, GORDAN GS. Antitumor efficacy of prednisone and sodium liothyronine in advanced breast cancer. *Cancer.* 15:334-7.
12. Amarante M, Watanabe M. The possible involvement of virus in breast cancer. *J Cancer Res Clin Oncol.* 2008. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19009309> [Accessed December 11, 2008].

13. Perrine SP, Hermine O, Small T, et al. A phase 1/2 trial of arginine butyrate and ganciclovir in patients with Epstein-Barr virus-associated lymphoid malignancies. *Blood*. 2007;109(6):2571-8.
14. Oertel SH, Riess H. Antiviral treatment of Epstein-Barr virus-associated lymphoproliferations. *Recent Results Cancer Res*. 2002;159:89-95.
15. Mentzer SJ, Fingerroth J, Reilly JJ, Perrine SP, Faller DV. Arginine butyrate-induced susceptibility to ganciclovir in an Epstein-Barr-virus-associated lymphoma. *Blood Cells Mol Dis*. 1998;24(2):114-23.
16. Mentzer SJ, Perrine SP, Faller DV. Epstein--Barr virus post-transplant lymphoproliferative disease and virus-specific therapy: pharmacological re-activation of viral target genes with arginine butyrate. *Transpl Infect Dis*. 2001;3(3):177-85.
17. Faller DV, Mentzer SJ, Perrine SP. Induction of the Epstein-Barr virus thymidine kinase gene with concomitant nucleoside antivirals as a therapeutic strategy for Epstein-Barr virus-associated malignancies. *Curr Opin Oncol*. 2001;13(5):360-7.
18. Goldstein JA. Cimetidine, ranitidine, and Epstein-Barr virus infection. *Ann Intern Med*. 1986;105(1):139.
19. Goldstein JA. Treatment of chronic Epstein-Barr virus disease with H2 blockers. *J Clin Psychiatry*. 1986;47(11):572.
20. Zagon IS, Donahue RN, Rogosnitzky M, McLaughlin PJ. Imiquimod upregulates the opioid growth factor receptor to inhibit cell proliferation independent of immune function. *Exp Biol Med (Maywood)*. 2008;233(8):968-79.
21. Gupta AK, Browne M, Bluhm R. Imiquimod: a review. *J Cutan Med Surg*. 6(6):554-60.
22. Hober D, Ajram L, Chehadeh W, et al. [Mechanisms of imiquimod indirect antiviral activity]. *Ann Biol Clin (Paris)*. 63(2):155-63.
23. Gupta AK, Cherman AM, Tyring SK. Viral and nonviral uses of imiquimod: a review. *J Cutan Med Surg*. 8(5):338-52.
24. Gupta AK, Cherman AM, Tyring SK. Viral and nonviral uses of imiquimod: a review. *J Cutan Med Surg*. 8(5):338-52.
25. Majewski S, Marczak M, Mlynarczyk B, Benninghoff B, Jablonska S. Imiquimod is a strong inhibitor of tumor cell-induced angiogenesis. *Int J Dermatol*. 2005;44(1):14-9.
26. Savage P, Horton V, Moore J, et al. A phase I clinical trial of imiquimod, an oral interferon inducer, administered daily. *Br J Cancer*. 1996;74(9):1482-6.
27. Witt PL, Ritch PS, Reding D, et al. Phase I trial of an oral immunomodulator and interferon inducer in cancer patients. *Cancer Res*. 1993;53(21):5176-80.
28. Sidky YA, Borden EC, Weeks CE, et al. Inhibition of murine tumor growth by an interferon-inducing imidazoquinolinamine. *Cancer Res*. 1992;52(13):3528-33.

29. Hasebe Y, Thomson LR, Dorey CK. Pentoxifylline inhibition of vasculogenesis in the neonatal rat retina. *Invest Ophthalmol Vis Sci.* 2000;41(9):2774-8.
30. Amirhosravi A, Meyer T, Warnes G, et al. Pentoxifylline inhibits hypoxia-induced upregulation of tumor cell tissue factor and vascular endothelial growth factor. *Thromb Haemost.* 1998;80(4):598-602.
31. Futakuchi M, Ogawa K, Tamano S, Takahashi S, Shirai T. Suppression of metastasis by nuclear factor kappaB inhibitors in an in vivo lung metastasis model of chemically induced hepatocellular carcinoma. *Cancer Sci.* 2004;95(1):18-24.
32. Coimbra R, Porcides RD, Melbostad H, et al. Nonspecific phosphodiesterase inhibition attenuates liver injury in acute endotoxemia. *Surg Infect (Larchmt).* 2005;6(1):73-85.
33. Chen Y, Ng Y, Lin S, et al. Pentoxifylline suppresses renal tumour necrosis factor-alpha and ameliorates experimental crescentic glomerulonephritis in rats. *Nephrol Dial Transplant.* 2004;19(5):1106-15.
34. Futakuchi M, Ogawa K, Tamano S, Takahashi S, Shirai T. Suppression of metastasis by nuclear factor kappaB inhibitors in an in vivo lung metastasis model of chemically induced hepatocellular carcinoma. *Cancer Sci.* 2004;95(1):18-24.
35. Berman B, Flores F, Burke G. Efficacy of pentoxifylline in the treatment of pruritic papular eruption of HIV-infected persons. *J Am Acad Dermatol.* 1998;38(6 Pt 1):955-9.
36. Deree J, Loomis WH, Wolf P, Coimbra R. Hepatic transcription factor activation and proinflammatory mediator production is attenuated by hypertonic saline and pentoxifylline resuscitation after hemorrhagic shock. *J Trauma.* 2008;64(5):1230-8; discussion 1238-9.
37. Koo DJ, Yoo P, Cioffi WG, et al. Mechanism of the beneficial effects of pentoxifylline during sepsis: maintenance of adrenomedullin responsiveness and downregulation of proinflammatory cytokines. *J Surg Res.* 2000;91(1):70-6.
38. Coimbra R, Porcides RD, Melbostad H, et al. Nonspecific phosphodiesterase inhibition attenuates liver injury in acute endotoxemia. *Surg Infect (Larchmt).* 2005;6(1):73-85.
39. Hernández E, Bucio L, Souza V, et al. Pentoxifylline downregulates alpha (I) collagen expression by the inhibition of IkappaBalpha degradation in liver stellate cells. *Cell Biol Toxicol.* 2008;24(4):303-14.
40. Ji Q, Zhang L, Jia H, Xu J. Pentoxifylline inhibits endotoxin-induced NF-kappa B activation and associated production of proinflammatory cytokines. *Ann Clin Lab Sci.* 2004;34(4):427-36.
41. Michetti C, Coimbra R, Hoyt DB, et al. Pentoxifylline reduces acute lung injury in chronic endotoxemia. *J Surg Res.* 2003;115(1):92-9.
42. Otani S, Kuinose M, Murakami T, et al. Preoperative oral administration of pentoxifylline ameliorates respiratory index after cardiopulmonary bypass through decreased production of IL-6. *Acta Med Okayama.* 2008;62(2):69-74.

43. Boldt J, Brosch C, Lehmann A, et al. Prophylactic use of pentoxifylline on inflammation in elderly cardiac surgery patients. *Ann Thorac Surg.* 2001;71(5):1524-9.
44. Çağlı K, Ulaş MM, Ozişik K, et al. The intraoperative effect of pentoxifylline on the inflammatory process and leukocytes in cardiac surgery patients undergoing cardiopulmonary bypass. *Perfusion.* 2005;20(1):45-51.
45. Tukov FF, Luyendyk JP, Ganey PE, Roth RA. The role of tumor necrosis factor alpha in lipopolysaccharide/ranitidine-induced inflammatory liver injury. *Toxicol Sci.* 2007;100(1):267-80.
46. Demir E, Paydas S, Balal M, et al. Effects of pentoxifylline on the cytokines that may play a role in rejection and resistive index in renal transplant recipients. *Transplant Proc.* 2006;38(9):2883-6.
47. Navarro J, Punzón MC, Pizarro A, et al. Pentoxifylline inhibits acute HIV-1 replication in human T cells by a mechanism not involving inhibition of tumour necrosis factor synthesis or nuclear factor-kappa B activation. *AIDS.* 1996;10(5):469-75.
48. Szebeni J. [A new drug in a new role: dipyridamole in the treatment of HIV-1 infections?]. *Orv Hetil.* 1991;132(35):1907-12.
49. Tonew E, Indulen MK, Dzeguze DR. Antiviral action of dipyridamole and its derivatives against influenza virus A. *Acta Virol.* 1982;26(3):125-9.
50. Korbecki M, Bankowski A, Filczak K, Klimek A. [Dipyridamole as an inhibitor of vaccinia virus replication]. *Mol Gen Mikrobiol Virusol.* 1985;(1):29-32.
51. Szebeni J, Wahl SM, Popovic M, et al. Dipyridamole potentiates the inhibition by 3'-azido-3'-deoxythymidine and other dideoxynucleosides of human immunodeficiency virus replication in monocyte-macrophages. *Proc Natl Acad Sci U S A.* 1989;86(10):3842-6.
52. Tenser RB, Gaydos A, Hay KA. Inhibition of herpes simplex virus reactivation by dipyridamole. *Antimicrob Agents Chemother.* 2001;45(12):3657-9.
53. Sakaguchi Y, Emi Y, Maehara Y, Kohnoe S, Sugimachi K. Combined treatment of adriamycin and dipyridamole inhibits lung metastasis of B16 melanoma cells in mice. *Eur Surg Res.* 1990;22(4):213-8.
54. Suzuki N, Oiwa Y, Sugano I, et al. Dipyridamole enhances an anti-proliferative effect of interferon in various types of human tumor cells. *Int J Cancer.* 1992;51(4):627-33.
55. Rhodes EL, Misch KJ, Edwards JM, Jarrett PE. Dipyridamole for treatment of melanoma. *Lancet.* 1985;1(8430):693.
56. Bando H, Yamashita T, Tsubura E. Effects of antiplatelet agents on pulmonary metastases. *Gann.* 1984;75(3):284-91.
57. Bastida E, del Prado J, Almirall L, Jamieson GA, Ordinas A. Inhibitory effects of dipyridamole on growth, nucleoside incorporation, and platelet-activating capability in the U87MG and SKNMC human tumor cell lines. *Cancer Res.* 1985;45(9):4048-52.

58. Tsavaris N, Kosmas C, Polyzos A, et al. Leucovorin + 5-fluorouracil plus dipyridamole in leucovorin + 5-fluorouracil-pretreated patients with advanced colorectal cancer: a pilot study of three different dipyridamole regimens. *Tumori*. 87(5):303-7.
59. Surkina ID. [Antiviral and regulatory interferon-inducing effects of dipyridamole]. *Ter Arkh*. 2000;72(8):61-4.
60. Suzuki N, Oiwa Y, Sugano I, et al. Dipyridamole enhances an anti-proliferative effect of interferon in various types of human tumor cells. *Int J Cancer*. 1992;51(4):627-33.
61. Damle BD, Sridhar R, Desai PB. Dipyridamole modulates multidrug resistance and intracellular as well as nuclear levels of doxorubicin in B16 melanoma cells. *Int J Cancer*. 1994;56(1):113-8.
62. Damle B, Desai P. Dipyridamole reverses the resistance to topoisomerase II inhibitors but not to antimicrotubule agents in multidrug-resistant melanoma cells. *Oncol Res*. 1994;6(2):49-57.
63. Desai PB, Duan J, Sridhar R, Damle BD. Reversal of doxorubicin resistance in multidrug resistant melanoma cells in vitro and in vivo by dipyridamole. *Methods Find Exp Clin Pharmacol*. 1997;19(4):231-9.
64. Stenkvis B. A possible new principle for adjuvant treatment of cancer in humans revealed by image analysis cytology. *Anal Quant Cytol Histol*. 2002;24(5):303-4.
65. Stenkvis B, Pengtsson E, Dahlqvist B, et al. Cardiac glycosides and breast cancer, revisited. *N Engl J Med*. 1982;306(8):484.
66. Newman RA, Yang P, Pawlus AD, Block KI. Cardiac glycosides as novel cancer therapeutic agents. *Mol Interv*. 2008;8(1):36-49.
67. Goldin AG, Safa AR. Digitalis and cancer. *Lancet*. 1984;1(8386):1134.
68. López-Lázaro M. Digitoxin as an anticancer agent with selectivity for cancer cells: possible mechanisms involved. *Expert Opin Ther Targets*. 2007;11(8):1043-53.
69. Haux J. Digitoxin is a potential anticancer agent for several types of cancer. *Med Hypotheses*. 1999;53(6):543-8.
70. Stenkvis B. Is digitalis a therapy for breast carcinoma? *Oncol Rep*. 6(3):493-6.
71. Prassas I, Diamandis EP. Novel therapeutic applications of cardiac glycosides. *Nat Rev Drug Discov*. 2008;7(11):926-35.
72. Dorr RT. Interferon-alpha in malignant and viral diseases. A review. *Drugs*. 1993;45(2):177-211.
73. Chevaliez S, Pawlotsky J. Interferons and their use in persistent viral infections. *Handb Exp Pharmacol*. 2009;(189):203-41.
74. Finter NB, Chapman S, Dowd P, et al. The use of interferon-alpha in virus infections. *Drugs*. 1991;42(5):749-65.

75. Levin S, Hahn T, Rosenberg H, Bino T. Treatment of life-threatening viral infections with interferon alpha: pharmacokinetic studies in a clinical trial. *Isr J Med Sci*. 1982;18(4):439-46.
76. Ahn HY, Hadizadeh KR, Seul C, et al. Epigallocatechin-3 gallate selectively inhibits the PDGF-BB-induced intracellular signaling transduction pathway in vascular smooth muscle cells and inhibits transformation of sis-transfected NIH 3T3 fibroblasts and human glioblastoma cells (A172). *Mol Biol Cell*. 1999;10(4):1093-104.
77. Sachinidis A, Seul C, Seewald S, et al. Green tea compounds inhibit tyrosine phosphorylation of PDGF beta-receptor and transformation of A172 human glioblastoma. *FEBS Lett*. 2000;471(1):51-5.
78. Sachinidis A, Seul C, Seewald S, et al. Green tea compounds inhibit tyrosine phosphorylation of PDGF beta-receptor and transformation of A172 human glioblastoma. *FEBS Lett*. 2000;471(1):51-5.
79. Weber A, Neuhaus T, Skach RA, et al. Mechanisms of the inhibitory effects of epigallocatechin-3 gallate on platelet-derived growth factor-BB-induced cell signaling and mitogenesis. *FASEB J*. 2004;18(1):128-30.
80. Leong H, Mathur P, Greene G. Green tea catechins inhibit angiogenesis through suppression of STAT3 activation. *Breast Cancer Res Treat*. 2008. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18821062> [Accessed December 12, 2008].
81. Shankar S, Ganapathy S, Srivastava RK. Green tea polyphenols: biology and therapeutic implications in cancer. *Front Biosci*. 2007;12:4881-99.
82. Beaney RP, Gullan RW, Pilkington GJ. Therapeutic potential of antidepressants in malignant glioma: clinical experience with clomipramine. *J Clin Oncol (Meeting Abstracts)*. 2005;23(16_suppl):1535.
83. Pilkington GJ, Parker K, Murray SA. Approaches to mitochondrially mediated cancer therapy. *Semin Cancer Biol*. 2008;18(3):226-35.
84. Daley E, Wilkie D, Loesch A, et al. Chlorimipramine: a novel anticancer agent with a mitochondrial target. *Biochem Biophys Res Commun*. 2005;328(2):623-32.
85. Austin LS, Lydiard RB, Ballenger JC, et al. Dopamine blocking activity of clomipramine in patients with obsessive-compulsive disorder. *Biol Psychiatry*. 1991;30(3):225-32.
86. Bilir A, Erguven M, Oktem G, et al. Potentiation of cytotoxicity by combination of imatinib and chlorimipramine in glioma. *Int J Oncol*. 2008;32(4):829-39.
87. Rooprai HK, Christidou M, Pilkington GJ. The potential for strategies using micronutrients and heterocyclic drugs to treat invasive gliomas. *Acta Neurochir (Wien)*. 2003;145(8):683-90.
88. Pommerenke EW, Volm M. Reversal of doxorubicin-resistance in solid tumors by clomipramine. *In Vivo*. 9(2):99-101.
89. Xia Z, Bergstrand A, DePierre JW, Nässberger L. The antidepressants imipramine, clomipramine, and citalopram induce apoptosis in human acute

- myeloid leukemia HL-60 cells via caspase-3 activation. *J Biochem Mol Toxicol.* 1999;13(6):338-47.
90. Crocenzi FA, Sánchez Pozzi EJ, Pellegrino JM, et al. Beneficial effects of silymarin on estrogen-induced cholestasis in the rat: a study in vivo and in isolated hepatocyte couplets. *Hepatology.* 2001;34(2):329-39.
91. Fehér J, Láng I, Nékám K, et al. Effect of silibinin on the activity and expression of superoxide dismutase in lymphocytes from patients with chronic alcoholic liver disease. *Free Radic Res Commun.* 1987;3(6):373-7.
92. Dehmlow C, Erhard J, de Groot H. Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin. *Hepatology.* 1996;23(4):749-54.
93. Lettéron P, Labbe G, Degott C, et al. Mechanism for the protective effects of silymarin against carbon tetrachloride-induced lipid peroxidation and hepatotoxicity in mice. Evidence that silymarin acts both as an inhibitor of metabolic activation and as a chain-breaking antioxidant. *Biochem Pharmacol.* 1990;39(12):2027-34.
94. van Pelt JF, Verslype C, Crabbé T, Zaman Z, Fevery J. Primary human hepatocytes are protected against prolonged and repeated exposure to ethanol by silibinin-dihemisuccinate. *Alcohol Alcohol.* 38(5):411-4.
95. Schümann J, Prockl J, Kiemer AK, et al. Silibinin protects mice from T cell-dependent liver injury. *J Hepatol.* 2003;39(3):333-40.
96. Crocenzi FA, Roma MG. Silymarin as a new hepatoprotective agent in experimental cholestasis: new possibilities for an ancient medication. *Curr Med Chem.* 2006;13(9):1055-74.
97. Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. *Drugs.* 2001;61(14):2035-63.
98. Kim J, Jin Y, Park B, et al. Luteolin prevents PDGF-BB-induced proliferation of vascular smooth muscle cells by inhibition of PDGF beta-receptor phosphorylation. *Biochem Pharmacol.* 2005;69(12):1715-21.
99. Beck MA. Antioxidants and viral infections: host immune response and viral pathogenicity. *J Am Coll Nutr.* 2001;20(5 Suppl):384S-388S; discussion 396S-397S.
100. Beck MA, Kolbeck PC, Rohr LH, et al. Benign human enterovirus becomes virulent in selenium-deficient mice. *J Med Virol.* 1994;43(2):166-70.
101. Beck MA, Williams-Toone D, Levander OA. Coxsackievirus B3-resistant mice become susceptible in Se/vitamin E deficiency. *Free Radic Biol Med.* 2003;34(10):1263-70.
102. Liu X, Yin S, Li G. [Effects of selenium supplement on acute lower respiratory tract infection caused by respiratory syncytial virus]. *Zhonghua Yu Fang Yi Xue Za Zhi.* 1997;31(6):358-61.
103. Beck MA, Levander OA. Host nutritional status and its effect on a viral pathogen. *J Infect Dis.* 2000;182 Suppl 1:S93-6.

104. Gómez RM, Berría MI, Levander OA. Host selenium status selectively influences susceptibility to experimental viral myocarditis. *Biol Trace Elem Res.* 2001;80(1):23-31.
105. Soriano-Garcia M. Organoselenium compounds as potential therapeutic and chemopreventive agents: a review. *Curr Med Chem.* 2004;11(12):1657-69.
106. Beck MA. Selenium and host defence towards viruses. *Proc Nutr Soc.* 1999;58(3):707-11.
107. Beck MA. Selenium and vitamin E status: impact on viral pathogenicity. *J Nutr.* 2007;137(5):1338-40.
108. Beck MA, Levander OA, Handy J. Selenium deficiency and viral infection. *J Nutr.* 2003;133(5 Suppl 1):1463S-7S.
109. Di Bella M, Gamberini G, Tait A, Fabio U, Quaglio GP. Synthesis and antimicrobial activity of monoalkylcarbamic and thiocarbamic esters of 3-mercapto-1,2,4-benzothiadiazine-1,1-dioxide and of its Bz-derivatives. *Farmaco [Sci.* 1983;38(7):466-72.
110. Rayman MP, Rayman MP. The argument for increasing selenium intake. *Proc Nutr Soc.* 2002;61(2):203-15.