Pancreatic Cancer: Supplements Alongside Chemotherapy
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I am not an oncologist. I strongly advocate that my patients with cancer seek the professional advice of a board-certified oncologist. I am an integrative family physician and have extensive experience with helping patients and their families improve their health, their well-being, and their outcomes during and after the cancer journey. I keep abreast of the ever-growing medical literature focused on the interaction between cancer and nutrition, spirit, and lifestyle. I am a strong advocate of traditional oncology chemotherapy and radiation therapy, when indicated, and I believe that the best application of medical oncology incorporates optimal nutrition, appropriately selected supplements, acupuncture, yoga, massage, spiritual counseling, meditation, and exercise. My goal is to enhance the healing process.

I have compiled a list of supplements which I believe to be useful during chemotherapy treatment for pancreatic cancer. Following that list is a summary of the literature from which I form my rationale. Undoubtedly there are more substances that may also be of benefit. I believe that the cumulative effect of their use will be to decrease the rate of adverse events caused by chemotherapy, to thereby improve patient safety, and to enhance survival outcomes.

There are three issues here. One issue is the impact of such supplements on survival outcomes from the use of chemotherapy. The second issue is the potential to reduce adverse effects of chemotherapy and thereby improve patient well-being. The third issue has to do with prevention or delay of cancer recurrence. There has been much speculation about the possibility that certain supplements (namely antioxidants) may impair the effectiveness of chemotherapy; however the growing weight of scientific literature suggests strongly that this is not the case and that, in certain studies, the effectiveness of chemotherapy is actually improved. The reduction of adverse effects of chemotherapy is supported in the literature. The prevention of various cancers with certain dietary and lifestyle modifications and certain supplements is also supported. There is very clear evidence that quality of life is directly related to survival outcomes. It has been my clinical observation that, following this approach, quality of life is superior. I have not seen any unexpected treatment failures; on the contrary, the feedback about clinical outcomes has been favorable.

To the extent possible, the following literature pertains to pancreatic; however for the purpose of describing a rationale for use, some of the literature pertains to other cancers but instead are included in order to describe an effect in the setting of chemotherapy. Much of it is focused on tissue culture media or on animal models commonly used to ascertain information about the effect in humans. These are quite helpful in predicting a human effect but are not always so easily predictive. Large human clinical trials are much better than animal or human tissue studies for predicting effect but are
largely not yet available, so the use of many supplements alongside chemotherapy should be considered experimental.

Disclaimers:

1. Some of the information below includes excerpts of others’ writing and is not intended to be representative of flagrant plagiarism. Citations are given.
2. I do not have any financial incentive for prescribing supplements. While I do recommend that certain supplements come from a small list of specific manufacturers for quality control issues, one of our local pharmacies handles these accounts. I write supplement prescriptions – they are not covered by insurance but can be paid for with health savings accounts provided that a physicians’ prescription is obtained.
3. It is vitally important that patients dialogue with their medical and radiation oncologists and with their primary care physicians. The relationship between patient and physician is very important, and encouragement of open communication about supplement use is vital. This article does not substitute for such communication but, rather, should be use as a vehicle for facilitating dialogue.


Recommendations:

Dietary: Whole Food Diet. Increase fresh organic fruits (3 medium pieces) and green/red/yellow/purple vegetables (5 cups), Green Tea 4 cups per day, Soy from tofu/tempah/miso 10-25 grams per day (plus from Kudzu listed below), Decrease overall meat intake to 3-4 servings per week and include no red meat. Increase fish but avoid higher mercury-containing fish.
Juicing - carrots. beets. apples spirulina, berries, nuts, whey protein, add ice cream for calories, add wheat germ for beta glucan, ground flaxseed if constipated.

Exercise: 3-4 hours per week, preferably slightly out of breath with walking, hiking, running, skiing, swimming, or biking.

Supplements as follows

Coriolus (Mycoherb via Kan Herbs - Shitake Mushroom extract) 60 drops twice per day.
Kudzu root extract (source of genistein) (Kan Herbs 20 grams = 3ml ~ 100 drops) 100 drops once per day.
Plantioxidant (Thorne - Green Tea and other phyto-antioxidants – each capsule contains: bilberry 20mg, milk thistle 50mg, grape seed extract 20mg, green tea extract 50mg, quercetin 50mg) 3 capsules twice per day.
**Breast Health Complete** (Pure Encapsulations – dessicated broccoli concentrate – 3 capsules contain: Vitamin D3 400iu, folate 400mcg, selenium 100mcg, flaxseed 1250mg, Norway spruce 10mg, diinolylmethane complex 100mg, phophatidylcholine 25mg, green tea 100mg (standardized to 65% total tea catechins and 23% EGCG, turmeric 250mg (95% curcuminoids), broccoli sprout concentrate 20:1 whole plan 200mg, Vitamin C 30mg) 3 capsules per day.

**L-glutamine powder** (Thorne – 3.8 grams/scoop) 1-2 scoops in water by mouth 3 times per day.

**Curcumin** (Thorne 500mg/capsules) 2 capsules 2-4 times per day, 90, RF prn (take the highest dose tolerated up to max of 4000mg/day) – adverse effect most often is abdominal fullness or pain. This can be eaten in food as curry or mixed into a smoothie if capsules are not preferred. Dose of curcumin per tablespoon of turmeric varies from 250mg (standard) up to 7456 mg (concentrated - [http://purebulk.com/curcumin-95-turmeric-pe-1kg-p-360.html](http://purebulk.com/curcumin-95-turmeric-pe-1kg-p-360.html)). This is best absorbed when cooked with oil (coconut butter or olive oil preferred).

**Melatonin** – (Thorne 3mg per capsule) 3-21mg, depending on sleep tolerance. Start with 1 capsule at bedtime and increase by adding 1 capsule every 3 days until either reaching 21mg (7 capsules) or lesser maximum tolerated dose (too sleepy the next day or dream disturbed sleep are the common side effects). Can be changed to 5mg capsule to reduce number of capsules per night.

**Traditional Chinese Medicine** formula prescription based on Chinese Medicine Zu-Fang pattern diagnosis system in the setting of pending chemotherapy treatment. Formula chosen depends on history/exam.
**Background Information with citations listed**

**Medicinal mushrooms – Beta Glucan**

Medicinal mushrooms – more specifically the mycelium of various mushrooms – have been used for centuries to treat a variety of ailments of the immunological system. It is thought that the large polysaccharides called beta glucans are the “active ingredients” in these mushrooms. The most studied included coriolus (trancetes vercicolor, or turkey tail mushroom), shitake (lentinula), reishi (ganoderma), maitake (grifola), himematsutake (Agaricus blazei), cordyceps, flammulina, and chaga. Other sources of beta-glucan include isolates from yeast or barley. In the setting of cancer, I rely mostly on coriolus, shitake, maitake, and himematsutake.

**Coriolus Versicolor – more scientific information at MD Anderson Cancer Center Website. Follow this link (click and paste into browser):**


**Coriolus (aka: PSP or PSK) does not interact with CYP 3A4, which is important, since over 60% of all pharmaceuticals are metabolized by this pathway.** “A clinical study was to investigate the ability of PSP to inhibit or induce the drug metabolism of CYP450 3A 4 in healthy adult human subjects by using a diagnostic CYP450 3A4 specific assay, the erythromycin breath test (EBT). The 14-day course of PSP in 12 healthy subjects (eight women and four men) was not associated with any clinically significant CYP450 3A4 inhibition or induction. This suggests that administration of PSP with other medications and dietary supplements which are primarily metabolized by the CYP450 3A4 pathway is not expected to be associated with significant herb-drug interactions.”


**Coriolus has no toxicity and no known drug interactions. It has been shown, in combination with chemotherapy, to increase survival rates in studies of cancer of the breast, lung, and stomach.** These were randomized studies of 540, 185, and 262 patients, respectively. Other studies showed increases in NK activity and number, IL2, and CD4/CD8 levels in the coriolus treated groups. One study of 359 breast cancer patients and one study of 65 hepatocellular cancer patients did not show a difference in survival between treatment and control groups. No adverse effects or interactions were observed.


Soy (Genistein is one of the principal soy isoflavones)

Genistein enhances efficacy of gemcitabine in pancreatic cancer cells in vitro and in vivo.

“We conducted our studies using paired isogenic human pancreatic cancer cell line with differences in metastatic behavior (COLO 357 and L3.6pl). In vitro studies were done to measure growth inhibition and degree of apoptotic cell death induced by either genistein alone, gemcitabine alone, or genistein followed by gemcitabine. Our results show that pretreatment of cells with genistein for 24 hours followed by gemcitabine resulted in 60% to 80% growth inhibition compared with 25% to 30% when gemcitabine was used alone… In addition to in vitro results, we show here for the first time, that genistein in combination with gemcitabine is much more effective as an antitumor agent compared with either agent alone in our orthotopic tumor model. But most importantly, our data also showed that a specific target, such as NF-κB, was inactivated in genistein-treated animal tumors and that gemcitabine-induced activation of NF-κB was completely inhibited in animal tumors treated with genistein and gemcitabine.”


Genistein enhances efficacy of gemcitabine and erlotinib in human pancreatic cell lines.

This human tissue study concludes, “Genistein potentiates the growth inhibition and apoptosis induced by erlotinib (Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor) and gemcitabine in certain pancreatic cancer cells. Akt and NF-kappaB inhibition represents one of the mechanisms for the potentiation of erlotinib- and gemcitabine-induced cell death by genistein.”


Genistein inhibits chemotherapy-induced NFkB activation (including activation by gemcitabine) in mouse study.

Genistein inhibits angiogenesis in pancreatic cancer cells by blocking HIF-1 and thereby reducing genetic expression of VEGF.

BACKGROUND: Previous reports indicate that Genistein, a naturally occurring isoflavonoid, exhibits strong antiangiogenic activity. The underlying mechanism of inhibition, however, remains unclear. Among the biologic effects of Genistein are the inhibition of tyrosine kinases and the inhibition of hypoxic activation of hypoxia-inducible factor-1 (HIF-1), one of the main regulators of VEGF gene expression.

METHODS: Hypoxic cell culture was performed in a modular incubator chamber. Vascular endothelial growth factor (VEGF) protein secretion was measured using the enzyme-linked immunosorbent assay, binding of DNA by HIF-1 was measured using the electrophoretic mobility shift assay, and mRNA quantification was performed using Northern blot analysis. Pancreatic carcinoma was studied in an orthotopic murine model. Angiogenesis in vivo was quantified by staining xenograft tumors for endothelial cell markers. RESULTS: VEGF protein secretion was dose-dependently suppressed with increasing doses of Genistein. Furthermore, treatment of pancreatic carcinoma cells with Genistein led to impaired activation of HIF-1 under hypoxic culture conditions. Northern blot analysis indicated that VEGF mRNA expression decreased upon treatment with Genistein, both under normoxic and hypoxic culture conditions. In vivo, Genistein inhibited tumor growth for xenograft pancreatic carcinoma cells, whereas extensive hypoxia was observed in xenograft tumors and was not influenced by Genistein therapy. Similarly, decreased VEGF mRNA levels were observed in Genistein-treated Capan-1 xenograft tumors.

CONCLUSIONS: The current study indicates that the previously reported antiangiogenic activity of Genistein probably is mediated by the inhibition of HIF-1, an important regulator of VEGF gene homeostasis, particularly under low-oxygen conditions. Therefore, this bioactive compound may well be beneficial to patients with pancreatic carcinoma.

Büchler P et al. Antiangiogenic activity of genistein in pancreatic carcinoma cells is mediated by the inhibition of hypoxia-inducible factor-1 and the down-regulation of VEGF gene expression. Cancer. 2004 Jan 1;100(1):201-10

Genistein reduces NFkB expression and activity in pancreatic, breast, lung, and prostate cancer cells in the setting of treatment with docetaxel, doxorubicin, and cisplatin. This reduction in NFkB activity is associated with control of tumor growth and apoptosis.

Cancer chemotherapeutic strategies commonly require multiple agents. However, use of multiple agents contributes to added toxicity resulting in poor treatment outcome. Thus, combination chemotherapy must be optimized to increase tumor response and at the same time lower its toxicity. Chemotherapeutic agents are known to induce nuclear factor kappaB (NF-kappaB) activity in tumor cells, resulting in lower cell killing and drug resistance. In contrast, genistein has been shown to inhibit the activity of NF-kappaB and the growth of various cancer cells without causing systemic toxicity. We therefore investigated whether the inactivation of NF-kappaB by genistein before treatment of various cancer cells with chemotherapeutic agents could lead to better tumor cell killing as tested by in vitro studies using gene transfections and also by animal studies. PC-3 (prostate), MDA-MB-231 (breast), H460 (lung), and BxPC-3 (pancreas) cancer cells were pretreated with 15 to 30 micromol/L genistein for 24 hours and then exposed to low doses of chemotherapeutic agents for an additional 48 to 72 hours. We found that 15 to
30 micromol/L genistein combined with 100 to 500 nmol/L cisplatin, 0.5 to 2 nmol/L docetaxel, or 50 ng/mL doxorubicin resulted in significantly greater inhibition of cell growth and induction of apoptosis compared with either agent alone. Moreover, we found that the NF-kappaB activity was significantly increased within 2 hours of cisplatin and docetaxel treatment and that the NF-kappaB inducing activity of these agents was completely abrogated in cells pretreated with genistein. These results were also supported, for the first time, by animal experiments, p65 cDNA transfection and p65 small interfering RNA studies, which clearly showed that a specific target (NF-kappaB) was affected in vivo. Collectively, our results clearly suggest that genistein pretreatment inactivates NF-kappaB and may contribute to increased growth inhibition and apoptosis induced by cisplatin, docetaxel, and doxorubicin in prostate, breast, lung, and pancreatic cancer cells. These results warrant carefully designed clinical studies investigating the combination of soy isoflavones and commonly used chemotherapeutic agents for the treatment of human cancers.


Genistein reduces NFkB activity in the setting of docetaxel and cisplatin. This reduction in NFkB activity is associated with control of tumor growth and apoptosis.

Cancer chemotherapeutic strategies should be devised to provide higher tumor response and lower toxicity for combination chemotherapy. Genistein has been shown to inhibit the growth of various cancer cells in vitro and in vivo without toxicity to normal cells. The antitumor effects of genistein could be in part due to inactivation of NF-kappaB activity. In contrast, chemotherapeutic agents inadvertently induce NF-kappaB activity, which may lead to chemoresistance. In this study, we investigated whether the inactivation of NF-kappaB by genistein would enhance the efficacy of chemotherapeutic agents. BxPC-3 pancreatic cancer cells were pretreated with 30 micromol/L genistein for 24 hours and then exposed to lower concentrations of chemotherapeutic agents for an additional 24 hours. Cell growth inhibition assay, apoptosis assay, and NF-kappaB EMSA were performed. The combination of 30 micromol/L genistein with 1 nmol/L docetaxel or 100 nmol/L cisplatin elicited significantly greater inhibition of cell growth compared with either agent alone. The combination treatment induced more apoptosis in BxPC-3 cells compared with single agents. Moreover, the NF-kappaB activity was significantly increased within 2 hours of docetaxel or cisplatin treatment, and the NF-kappaB-inducing activity of these agents was completely abrogated in cells pretreated with genistein. These results clearly suggest that genistein pretreatment, which inactivates NF-kappaB activity, together with other cellular effects of genistein, may contribute to increased cell growth inhibition and apoptosis inducing effects of nontoxic doses of docetaxel and cisplatin, which could be a novel strategy for the treatment of pancreatic cancer.


Genistein causes apoptosis in human pancreatic cancer cells implanted in nude mice.
INTRODUCTION: The critical need for novel therapeutic approaches to pancreatic cancer treatment is clear. Genistein, a naturally occurring isoflavonoid, is active against certain solid malignancies, but its effect on pancreatic cancer is unknown. AIMS: To investigate the bioactivity of genistein in experimental pancreatic cancer in vitro and in vivo. METHODOLOGY: The effect of intraperitoneal genistein administration on local tumor growth and metastatic disease was determined in an orthotopic nude mouse model. Apoptosis in tumor specimens was determined by the terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end labeling (TUNEL) technique. In vitro, the effect of genistein on cell growth was assessed by cell count and MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) colorimetric assay. Apoptosis was determined in vitro by DNA laddering and annexin-V. Caspase-3 and nuclear factor-kappaB activity were measured following genistein treatment. RESULTS: In vivo, genistein significantly improved survival, almost completely inhibited metastasis, and increased apoptosis in an orthotopic model of pancreatic cancer. In vitro genistein treatment resulted in apoptosis in all pancreatic cancer cell lines tested, and this appeared to be mediated by activation of caspase-3. CONCLUSION: These findings suggest that the antimetastatic effect of genistein treatment in vivo is mediated by induction of apoptosis. Genistein may have a therapeutic benefit for patients with pancreatic cancer, in particular after surgery, to prevent recurrence of metastatic disease.

Genistein reduces metastases and contributes to longer survival time by inducing apoptosis in mice with metastatic pancreatic cancer.

Green Tea (EGCG - Epigallocatechin gallate)

EGCG from green tea inhibits growth, invasion, angiogenesis and metastasis of pancreatic cancer.
We have shown that epigallocatechin-3-gallate (EGCG), a polyphenolic compound from green tea, inhibits growth and induces apoptosis in human pancreatic cancer cells. However, the preclinical potential of EGCG in a suitable mouse model has not been examined. In this study, we examined the molecular mechanisms by which EGCG inhibited growth, invasion, metastasis and angiogenesis of human pancreatic cancer cells in a xenograft model system. EGCG inhibited viability, capillary tube formation and migration of HUVEC, and these effects were further enhanced in the presence of an ERK inhibitor. In vivo, AsPC-1 xenografted tumors treated with EGCG showed significant reduction in volume, proliferation (Ki-67 and PCNA staining), angiogenesis (vWF, VEGF and CD31) and metastasis (MMP-2, MMP-7, MMP-9 and MMP-12) and induction in apoptosis (TUNEL), caspase-3 activity and growth arrest (p21/WAF1). EGCG also inhibited circulating endothelial growth factor receptor 2 (VEGF-R2) positive endothelial cells derived from xenografted mice. Tumor samples from EGCG treated mice showed significantly reduced ERK activity, and enhanced p38 and JNK activities. Overall, our data suggest that EGCG inhibits pancreatic cancer growth, invasion,
metastasis and angiogenesis, and thus could be used for the management of pancreatic cancer prevention and treatment.

**Green Tea acts differently in tumor cells than in normal cells. It induces oxidative stress in tumor cells but reduces oxidative stress in normal cells. This suggests an explanation as to why green tea is a powerful antioxidant but does not interfere with the efficacy of chemotherapy.**

Green tea polyphenols (GTPPs) are considered beneficial to human health, especially as chemopreventive agents. Recently, cytotoxic reactive oxygen species (ROS) were identified in tumor and certain normal cell cultures incubated with high concentrations of the most abundant GTPP, (-)-epigallocatechin-3-gallate (EGCG). If EGCG also provokes the production of ROS in normal epithelial cells, it may preclude the topical use of EGCG at higher doses. The current study examined the oxidative status of normal epithelial, normal salivary gland, and oral carcinoma cells treated with EGCG, using ROS measurement and catalase and superoxide dismutase activity assays. The results demonstrated that high concentrations of EGCG induced oxidative stress only in tumor cells. In contrast, EGCG reduced ROS in normal cells to background levels. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay and 5-bromodeoxyuridine incorporation data were also compared between the two oral carcinoma cell lines treated by EGCG, which suggest that a difference in the levels of endogenous catalase activity may play an important role in reducing oxidative stress provoked by EGCG in tumor cells. It is concluded that pathways activated by GTPPs or EGCG in normal epithelial versus tumor cells create different oxidative environments, favoring either normal cell survival or tumor cell destruction. This finding may lead to applications of naturally occurring polyphenols to enhance the effectiveness of chemo/radiation therapy to promote cancer cell death while protecting normal cells.

**In another example of antioxidants behaving differently in normal versus tumor tissue, grape seed extract is shown to increase VEGF (vascular endothelial growth factor) in the setting of healing wounds of normal skin, whereas it is also known to decrease TNF-alpha-induced VEGF gene expression in cancer cells.**

**Green Tea for Pancreatic Cancer Prevention** - In one large-scale clinical study researchers compared green tea drinkers with non-drinkers and found that those who drank the most tea were significantly less likely to develop pancreatic cancer. This was particularly true for women -- those who drank the most green tea were half as likely to develop pancreatic cancer as those who drank less tea. Men who drank the most tea were 37% less likely to develop pancreatic cancer. However, it is not clear from this...
EGCG, a major component of green tea, inhibits tumor growth by inhibiting VEGF induction in human colon carcinoma cells implanted in mice.
Catechins are key components of teas that have antiproliferative properties. We investigated the effects of green tea catechins on intracellular signalling and VEGF induction in vitro in serum-deprived HT29 human colon cancer cells and in vivo on the growth of HT29 cells in nude mice. In the in vitro studies, (-)epigallocatechin gallate (EGCG), the most abundant catechin in green tea extract, inhibited Erk-1 and Erk-2 activation in a dose-dependent manner. However, other tea catechins such as (-)epigallocatechin (EGC), (-)epicatechin gallate (ECG), and (-)-epicatechin (EC) did not affect Erk-1 or 2 activation at a concentration of 30 microM. EGCG also inhibited the increase of VEGF expression and promoter activity induced by serum starvation. In the in vivo studies, athymic BALB/c nude mice were inoculated subcutaneously with HT29 cells and treated with daily intraperitoneal injections of EC (negative control) or EGCG at 1.5 mg day(-1)mouse(-1) starting 2 days after tumour cell inoculation. Treatment with EGCG inhibited tumour growth (58%), microvessel density (30%), and tumour cell proliferation (27%) and increased tumour cell apoptosis (1.9-fold) and endothelial cell apoptosis (3-fold) relative to the control condition (P< 0.05 for all comparisons). EGCG may exert at least part of its anticancer effect by inhibiting angiogenesis through blocking the induction of VEGF.


Green tea inhibits tumor growth by reducing levels of VEGF in breast cancer cell line.

Cruciferous Vegetables (broccoli, cauliflower, Brussels sprouts, etc)
Note: Most research focuses on one of four active components of this food group: indole-3-carbinol, diindolylmethane, sulforaphane, and calcium-d-glucarate. As the sum total of such studies is positive, I rely on the whole food source itself, rather than any one of the extracted active components. For this reason, I use Breast Health Complete by Pure Encapsulations.

Diindolylmethane (from broccoli and other cruciferous vegetables) is synergistic with paclitaxel for treating breast cancer.
HER2 / neu positive breast tumors are difficult to treat. About 25 to 30% of invasive breast tumors overexpress the HER2 / neu oncogene. These tumors are aggressive and become resistant to chemotherapeutic drugs. 3'3'-diindolylmethane (DIM), the active metabolite of indole-3-carbinol, a naturally occurring compound found in cruciferous vegetables, has been found to have anti-cancer properties in both humans and animals. DIM has been shown to induce cell cycle arrest and apoptosis in animal breast cancer models. CONCLUSIONS: Diindolylmethane in combination with paclitaxel synergistically inhibits growth of Her2 / neu human breast cancer cells through G2M
phase cell-cycle arrest and induction of apoptosis / necrosis. The Her2 / neu receptor and its downstream signaling protein ERK1/2 appear to be involved in DIM's affect on cell growth and differentiation, whereas apoptosis appears to be mediated through the mitochondrial pathway (Bcl-2/PARP). It appears diindolylmethane, a naturally occurring, nontoxic compound, may be a beneficial addition to a traditional (taxane-based) chemotherapy regimen.


**Sulforaphane (from broccoli and other cruciferous vegetables) promotes apoptosis of pancreatic cancer cells by inhibiting NFkB binding and by downregulating other apoptosis inhibitors.**

**BACKGROUND AND AIMS:** Emerging evidence suggests that highly treatment-resistant tumour-initiating cells (TICs) play a central role in the pathogenesis of pancreatic cancer. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) is considered to be a novel anticancer agent; however, recent studies have shown that many pancreatic cancer cells are resistant to apoptosis induction by TRAIL due to TRAIL-activated nuclear factor-kappaB (NF-kappaB) signalling. Several chemopreventive agents are able to inhibit NF-kappaB, and favourable results have been obtained--for example, for the broccoli compound sulforaphane--in preventing metastasis in clinical studies. The aim of the study was to identify TICs in pancreatic carcinoma for analysis of resistance mechanisms and for definition of sensitising agents.**

**METHODS:** TICs were defined by expression patterns of a CD44(+)/CD24(-), CD44(+)/CD24(+) or CD44(+)/CD133(+) phenotype and correlation to growth in immunodeficient mice, differentiation grade, clonogenic growth, sphere formation, aldehyde dehydrogenase (ALDH) activity and therapy resistance.**

**RESULTS:** Mechanistically, specific binding of transcriptionally active cRel-containing NF-kappaB complexes in TICs was observed. Sulforaphane prevented NF-kappaB binding, downregulated apoptosis inhibitors and induced apoptosis, together with prevention of clonogenicity. Gemcitabine, the chemopreventive agents resveratrol and wogonin, and the death ligand TRAIL were less effective. In a xenograft model, sulforaphane strongly blocked tumour growth and angiogenesis, while combination with TRAIL had an additive effect without obvious cytotoxicity in normal cells. Freshly isolated patient tumour cells expressing markers for TICs could be sensitised by sulforaphane for TRAIL-induced cytotoxicity.**

**CONCLUSION:** The data provide new insights into resistance mechanisms of TICs and suggest the combination of sulforaphane with TRAIL as a promising strategy for targeting of pancreatic TICs.


**Glutamine**

**Glutamine decreases neuropathy caused by paclitaxel and several other adverse effects of various chemotherapy agents.**

Malignancy produces a state of physiologic stress that is characterized by a relative deficiency of glutamine, a condition that is further exacerbated by the effects of cancer treatment. Glutamine deficiency may impact on normal tissue tolerance to antitumor
treatment, and may lead to dose reductions and compromised treatment outcome. Providing supplemental glutamine during cancer treatment has the potential to abrogate treatment-related toxicity. We reviewed the available data on the use of glutamine to decrease the incidence and severity of adverse effects due to chemotherapy and/or radiation in cancer patients. METHODS: We performed a search of the MEDLINE database during the time period 1980-2003, and reviewed the English language literature of both human and animal studies pertaining to the use of glutamine in subjects with cancer. We also manually searched the bibliographies of published articles for relevant references. MAIN RESULTS: The available evidence suggests that glutamine supplementation may decrease the incidence and/or severity of chemotherapy-associated mucositis, irinotecan-associated diarrhea, paclitaxel-induced neuropathy, hepatic veno-occlusive disease in the setting of high dose chemotherapy and stem cell transplantation, and the cardiotoxicity that accompanies anthracycline use. Oral glutamine supplementation may enhance the therapeutic index by protecting normal tissues from, and sensitizing tumor cells to chemotherapy and radiation-related injury. CONCLUSIONS: The role of glutamine in the prevention of chemotherapy and radiation-induced toxicity is evolving. Glutamine supplementation is inexpensive and it may reduce the incidence of gastrointestinal, neurologic, and possibly cardiac complications of cancer therapy. Further studies, particularly placebo-controlled phase III trials, are needed to define its role in chemotherapy-induced toxicity. Savarese DM et al. Prevention of chemotherapy and radiation toxicity with glutamine. Cancer Treat Rev. 2003 Dec;29(6):501-13.

Glutamine reduces paclitaxel induced neuropathy in a small case-control trial.

Purpose: Dose-limiting toxicity of many newer chemotherapeutic agents is peripheral neuropathy. Prior attempts to reduce this side effect have been unsuccessful. We report on the possible successful reduction of peripheral neuropathy with glutamine administration after high-dose paclitaxel.

Experimental Design: Patients entered a high-dose chemotherapy protocol in which the first high-dose cycle was paclitaxel at 825 mg/m² given over 24 h. The first cohort of patients did not receive glutamine, and the second cohort of patients received glutamine at 10 g orally three times a day for 4 days starting 24 h after completion of paclitaxel. Neurological assessment was performed at baseline, and at least 2 weeks after paclitaxel, and consisted of a complete neurological exam and nerve conduction studies.

Results: There were paired pre- and post-paclitaxel evaluations on 33 patients who did not receive glutamine and 12 patients who did. The median interval between pre- and post-exams was 32 days. For patients who received glutamine, there was a statistically significant reduction in the severity of peripheral neuropathy as measured by development of moderate to severe dysesthesias and numbness in the fingers and toes (P < 0.05). The degree and incidence of motor weakness was reduced (56 versus 25%; P = 0.04) as well as deterioration in gait (85 versus 45%; P = 0.016) and interference with activities of daily living (85 versus 27%; P = 0.001). Moderate to severe paresthesias in the fingers and toes were also reduced (55 versus 42% and 64 versus 50%, respectively), although this value was not statistically significant. All of these toxicities were reversible over time.

Conclusions: Glutamine may reduce the severity of peripheral neuropathy associated with high-dose paclitaxel; however, results from randomized, placebo-controlled clinical trials
will be needed to fully assess its impact, if any. Trials are currently ongoing to assess its efficacy for standard-dose paclitaxel in breast cancer and other tumors for which peripheral neuropathy is the dose-limiting toxicity.


Another similar size trial of glutamine 10 grams three times per day for 5 days starting on the day of chemotherapy did not produce any improvement in paclitaxel-induced myalgia and arthralgia; this study did not assess for effect on neuropathy. There were no adverse effects caused by the glutamine.


**Curcumin**

Curcumin suppresses the paclitaxel-induced NFkB (Nuclear Factor-B) pathway in breast cancer cells and inhibits lung metastasis of human breast cancer cells implanted in nude mice.

Currently, there is no effective therapy for metastatic breast cancer after surgery, radiation, and chemotherapy have been used against the primary tumor. Because curcumin suppresses nuclear factor-B (NF-B) activation and most chemotherapeutic agents activate NF-B that mediates cell survival, proliferation, invasion, and metastasis, we hypothesized that curcumin would potentiate the effect of chemotherpay in advanced breast cancer and inhibit lung metastasis. We tested this hypothesis using paclitaxel (Taxol)-resistant breast cancer cells and a human breast cancer xenograft model. As examined by electrophoretic mobility gel shift assay, paclitaxel activated NF-B in breast cancer cells and curcumin inhibited it; this inhibition was mediated through inhibition of IB kinase activation and IB phosphorylation and degradation. Curcumin also suppressed the paclitaxel-induced expression of antiapoptotic (XIAP, IAP-1, IAP-2, Bcl-2, and Bcl-xL), proliferative (cyclooxygenase 2, c-Myc, and cyclin D1), and metastatic proteins (vascular endothelial growth factor, matrix metalloproteinase-9, and intercellular adhesion molecule-1). It also enhanced apoptosis. In a human breast cancer xenograft model, dietary administration of curcumin significantly decreased the incidence of breast cancer metastasis to the lung and suppressed the expression of NF-B, cyclooxygenase 2, and matrix metalloproteinase-9. Overall, our results indicate that curcumin, which is a pharmacologically safe compound, has a therapeutic potential in preventing breast cancer metastasis possibly through suppression of NF-B and NF-B–regulated gene products.

We found that curcumin did block paclitaxel-induced NF-B activation and NF-B–regulated gene expression in breast cancer cells and inhibited breast cancer metastasis to the lung in nude mice.


**Curcumin Augments Gemcitabine Cytotoxic Effect on Pancreatic Adenocarcinoma Cell Lines**

BACKGROUND AND AIM: Gemcitabine, the first-line agent in pancreatic adenocarcinoma, has shown limited clinical benefit. Cyclooxygenase-2 (COX-2)
represent one of the most promising targets for cancer prevention and treatment. In this study, we investigated whether the phytochemical curcumin, a natural COX-2 inhibitor, can potentiate gemcitabine effect on survival of human pancreatic cancer cells.

METHODS: P34 (high COX-2 expression) and Panc-1 (low COX-2 expression) pancreatic cancer cell lines were exposed to different concentrations of gemcitabine (0.1-10 microM), curcumin (0-50 microM), and their combination. Cell viability was evaluated by XTT assay. Cell cycle and apoptosis were assessed by flow cytometry. COX-2, EGFR, and p-ERK1/2 expression was measured by Western blot analysis.

RESULTS: Curcumin increased the inhibitory effect of gemcitabine on cell viability as well as its pro-apoptotic effect in COX-2 positive, p34 cells, but not in COX-2 negative, Panc-1 cells. In p34 cells, combination of curcumin and gemcitabine downregulated both COX-2 and p-ERK1/2 in a dose-dependent manner. CONCLUSION: The increased cytotoxic effect of the combination on cell survival and on the induction of apoptosis in COX-2 expressing pancreatic cancer cells is probably associated with downregulation of COX-2 and p-ERK1/2 levels. This finding may contribute to the development of an effective treatment of pancreatic adenocarcinoma.


Curcumin is well tolerated and has biological effects in patients with pancreatic cancer.

PURPOSE: Pancreatic cancer is almost always lethal, and the only U.S. Food and Drug Administration-approved therapies for it, gemcitabine and erlotinib, produce objective responses in <10% of patients. We evaluated the clinical biological effects of curcumin (diferuloylmethane), a plant-derived dietary ingredient with potent nuclear factor-kappaB (NF-kappaB) and tumor inhibitory properties, against advanced pancreatic cancer.

EXPERIMENTAL DESIGN: Patients received 8 g curcumin by mouth daily until disease progression, with restaging every 2 months. Serum cytokine levels for interleukin (IL)-6, IL-8, IL-10, and IL-1 receptor antagonists and peripheral blood mononuclear cell expression of NF-kappaB and cyclooxygenase-2 were monitored. RESULTS: Twenty-five patients were enrolled, with 21 evaluable for response. Circulating curcumin was detectable as drug in glucuronide and sulfate conjugate forms, albeit at low steady-state levels, suggesting poor oral bioavailability. Two patients showed clinical biological activity. One had ongoing stable disease for >18 months; interestingly, one additional patient had a brief, but marked, tumor regression (73%) accompanied by significant increases (4- to 35-fold) in serum cytokine levels (IL-6, IL-8, IL-10, and IL-1 receptor antagonists). No toxicities were observed. Curcumin down-regulated expression of NF-kappaB, cyclooxygenase-2, and phosphorylated signal transducer and activator of transcription 3 in peripheral blood mononuclear cells from patients (most of whom had baseline levels considerably higher than those found in healthy volunteers). Whereas there was considerable interpatient variation in plasma curcumin levels, drug levels peaked at 22 to 41 ng/mL and remained relatively constant over the first 4 weeks.

CONCLUSIONS: Oral curcumin is well tolerated and, despite its limited absorption, has biological activity in some patients with pancreatic cancer.

**Curcumin acts synergistically with Gemcitabine in an orthotopic model of pancreatic cancer by reducing cancer angiogenesis and growth via decreased gene expression of NFkB.**

Gemcitabine is currently the best treatment available for pancreatic cancer, but the disease develops resistance to the drug over time. Agents that can either enhance the effects of gemcitabine or overcome chemoresistance to the drug are needed for the treatment of pancreatic cancer. Curcumin, a component of turmeric (Curcuma longa), is one such agent that has been shown to suppress the transcription factor nuclear factor-kappaB (NF-kappaB), which is implicated in proliferation, survival, angiogenesis, and chemoresistance. In this study, we investigated whether curcumin can sensitize pancreatic cancer to gemcitabine in vitro and in vivo. In vitro, curcumin inhibited the proliferation of various pancreatic cancer cell lines, potentiated the apoptosis induced by gemcitabine, and inhibited constitutive NF-kappaB activation in the cells. In vivo, tumors from nude mice injected with pancreatic cancer cells and treated with a combination of curcumin and gemcitabine showed significant reductions in volume (P = 0.008 versus control; P = 0.036 versus gemcitabine alone), Ki-67 proliferation index (P = 0.030 versus control), NF-kappaB activation, and expression of NF-kappaB-regulated gene products (cyclin D1, c-myc, Bcl-2, Bcl-xL, cellular inhibitor of apoptosis protein-1, cyclooxygenase-2, matrix metalloproteinase, and vascular endothelial growth factor) compared with tumors from control mice treated with olive oil only. The combination treatment was also highly effective in suppressing angiogenesis as indicated by a decrease in CD31(+) microvessel density (P = 0.018 versus control). Overall, our results suggest that curcumin potentiates the antitumor effects of gemcitabine in pancreatic cancer by suppressing proliferation, angiogenesis, NF-kappaB, and NF-kappaB-regulated gene products.


**Melatonin**

Melatonin appears to decrease neuropathy caused by paclitaxel.

Neurotoxicity caused by taxane chemotherapies (CT) can be dose limiting and can cause a decrease in quality of life. Melatonin has been evaluated for its use in decreasing adverse reactions of CT. Preclinical data suggests that melatonin has neuroprotective capability. The objective of this study is to determine if melatonin will decrease the incidence and severity of taxane-related neuropathy. **Methods:** Fifty patients beginning CT for any stage of breast cancer with paclitaxel, albumin-bound paclitaxel, or docetaxel will be enrolled. Patients should have no underlying neuropathy. Melatonin is given at 21 mg at bedtime on Day 1 and continued for 28 days after the last taxane dose. Every 28 days, neuropathy is assessed using the NCI-CTC 3.0 scale and possible side effects of melatonin are evaluated. Quality of life (QOL) is analyzed using the FACT-Taxane QOL assessment. Outcomes analyzed included the incidence and severity of neuropathy, and changes in QOL. **Results:** Currently 17 patients have been enrolled with 12 having completed taxaneCT and melatonin. Five have withdrawn due to non-medical reasons and were evaluated for toxicities. The mean age is 49 years (range 36-67 years). The end of study FACT-Taxane score was available for 11 of the 12 patients, with an average score of 135 (range 106-168). The average baseline QOL score was 131 (range 99-148).
The average change in QOL score was +4. Eleven have completed paclitaxel with an average dose of 862 mg/m² (range 525-1620 mg/m²). One patient received docetaxel t 450 mg/m². Five patients self-reported adverse effects including night-time sedation (2), hot flashes (1), headache (1), constipation (1), nail darkening (1), and fatigue (1). Neuropathy distribution was as follows: 50% (6) of patients had grade 0, 33% (4) grade 1, and 16% (2) grade 2 neuropathy. The mean change in neuropathy score was +0.67.

**Conclusion:** Melatonin appears promising as a neuroprotective agent in patients receiving taxane-based chemotherapy. No patient developed grade 3 or 4 neuropathy compared to historical controls of 22-33%. Fifty percent of patients treated with melatonin while on taxane CT developed no neuropathy, and those who did, had grade 1 or 2 neuropathy. QOL was maintained. Melatonin's neuroprotective effect should be further evaluated.


**Melatonin supplementation (20 mg per day) has decreased toxicity and improved effectiveness of chemotherapy with paclitaxel.**


**Other**

**Human pancreatic cell lines in culture medium are reduced when exposed to Vitamin A and Vitamin D but not with Vitamins E or K.**

BACKGROUND: The four fat-soluble vitamins A, D, E and K have been tested in experimental and human studies to assess their influence on the growth of cancer cells of different origins. Receptors for vitamin A and D have been detected on pancreatic cancer cells, and analogues of these reduced the cell number in vitro. The aim of the present study was to evaluate the effect of fat-soluble vitamins on the growth of pancreatic cancer cells. METHODS: The seven cell lines used were established from patients operated on for pancreatic adenocarcinoma. The effect of incubation with the vitamin A analogues all-trans-retinoic acid (atRA; tretinoin) and 9-cis-retinoic acid (9-cis-RA), the synthetic vitamin D analogue EB 1089, vitamin E succinate and K on the cell number was examined by the XTT method. RESULTS: The vitamin A and D analogues decreased the pancreatic cancer cell number when high concentrations of 10 - 10 M were administered. A combination of retinoids and the vitamin D analogue EB 1089 did not enhance the effect. Vitamin E succinate inhibited cell growth to a small extent (maximal 26%) in 3 out of 7 cell lines, whereas vitamin K increased the pancreatic cancer cell number in 3 out of 7 cell lines. CONCLUSION: High concentrations of vitamin A and D analogues decreased the cell number in pancreatic cancer cell lines. Vitamin E succinate and K did not have this effect. In the treatment of pancreatic cancer, further exploration of vitamin D analogues could be fruitful.

Cancer cell lines from the breast, lung, pancreas, and prostate had their growth reduced by extracts of 12 Chinese herbs.

Aqueous extracts of 12 Chinese medicinal herbs, Anemarrhena asphodeloides, Artemisia argyi, Commiphora myrrha, Duchesnea indica, Gleditsia sinensis, Ligustrum lucidum, Rheum palmatum, Rubia cordifolia, Salvia chinensis, Scutellaria barbata, Uncaria rhyynchophylla and Vaccaria segetalis were evaluated for their antiproliferative activity on eight cancer cell lines as well as on normal human mammary epithelial cells. Five human and three murine cancer cell lines representing different tissues (breast, lung, pancreas and prostate) were used. All the crude aqueous extracts demonstrated growth inhibitory activity on some or all of the cancer cell lines, but only two showed activity against the normal mammary epithelial cells. Overall, the murine cell lines tended to be more sensitive to most of the extracts compared with the human cell lines. Among the human cell lines, cell type specificity was observed for two extracts. These results indicate the potential use of traditional Chinese medicinal herbs as antineoplastic agents and suggest that further studies evaluating their mechanism(s) of action and the isolation of active antitumor compounds are warranted.


**Vitamin C:** While no citation is listed here, I have reviewed the literature on this issue in the past. My conclusion is that oral vitamin C is unlikely to produce serum levels adequate to significantly alter tumor growth. However, I do believe that the balance of literature is favorably on the side of high dose intravenous Vitamin C in cases in which there is either failure of conventional treatment or in which conventional oncology has nothing to offer. I also believe that studies will be forthcoming in the next decade which will vindicate the concurrent use of high dose vitamin C alongside various chemotherapy regimens. However, at this point, the literature is at the mechanism/tissue study phase and includes interesting anecdotal case reports.

**Fish Oil has no effect (negatively or positively) on the antitumor effect of gemcitabine. It does reduce the incidence of cardiovascular disease and should be taken with antioxidants (either in the diet or via supplement).** While there are a number of studies showing appropriate use with radiation and other chemotherapeutic agents, I can find no studies of effect on paclitaxel nor studies of use exclusively in pancreatic cancer.

**BACKGROUND:** n-3 fatty acids are increasingly being administered to cancer patients for the treatment of cachexia, and it is thus important to know of any potential interactions with ongoing cytotoxic drug therapy. **MATERIALS AND METHODS:** For this reason eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were administered to mice bearing the cachexia-inducing MAC16 colon adenocarcinoma, and the effect of epothilone, gemcitabine, 5-fluorouracil and cyclophosphamide on tumour growth and body weight determined. **RESULTS:** Epothilone alone had a minimal effect on tumour growth rate, but this was potentiated by DH4, while for 5-fluorouracil and cyclophosphamide tumour growth inhibition was enhanced by EPA. The antitumour effect of gemcitabine was not altered by either fatty acid. EPA arrested the development
of cachexia, while DHA had no effect and the same was true for their effect on tumour growth rate. The anticachectic effect of EPA was only seen in combination with 5-fluorouracil. CONCLUSION: These results suggest that n-3 fatty acids do not interfere with the action of chemotherapy and may potentiate the effect of certain agents.