

Evidence-based complementary treatment of pancreatic cancer: a review of adjunct therapies including paricalcitol, hydroxychloroquine, intravenous vitamin C, statins, metformin, curcumin, and aspirin

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Abstract: Despite new and exciting research and renewed optimism about future therapy, current statistics of survival from pancreatic cancer remains dismal. Patients seeking alternative or complementary treatments should be warned to avoid the hype and instead look to real science. A variety of relatively safe and inexpensive treatment options that have shown success in preclinical models and/or retrospective studies are currently available. Patients require their physicians to provide therapeutic guidance and assistance in obtaining and administering these various therapies. Paricalcitol, an analog of vitamin D, has been shown by researchers at the Salk Institute for Biological Studies to break through the protective stroma surrounding tumor cells. Hydroxychloroquine has been shown to inhibit autophagy, a process by which dying cells recycle injured organelles and internal toxins to generate needed energy for survival and reproduction. Intravenous vitamin C creates a toxic accumulation of hydrogen peroxide within cancer cells, hastening their death. Metformin inhibits mitochondrial oxidative metabolism utilized by cancer stem cells. Statins inhibit not only cholesterol but also other factors in the same pathway that affect cancer cell growth, protein synthesis, and cell cycle progression. A novel formulation of curcumin may prevent resistance to chemotherapy and inhibit pancreatic cancer cell proliferation. Aspirin therapy has been shown to prevent pancreatic cancer and may be useful to prevent recurrence. These therapies are all currently available and are reviewed in this paper with emphasis on the most recent laboratory research and clinical studies.

Keywords: vitamin D, autophagy, stroma, T cells, integrative medicine, supplements, stellate cell

Background

Despite new, exciting research and renewed optimism about future therapy, current statistics of survival from pancreatic cancer remains dismal. Certainly, patients should be encouraged to join clinical trials where opportunities for better outcomes exist, while supporting the critical cause of advancing the state of cancer treatment for all. Unfortunately, for many patients, clinical trials remain unavailable or impractical, and in fact, only 4% of all pancreatic cancer patients are enrolled in trials. Patients should be given the opportunity to design their own trial with currently available experimental treatments, particularly those that have shown promise in preclinical trials, many of which have already advanced to early-phase human trials.

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Patients seeking “alternative” treatments should be warned to avoid hype and instead look to real science. These treatments should never be used as replacement for recommended treatments such as surgery or chemotherapy, but, rather, to supplement them. Certainly, physicians should provide patients with all the proper warnings in regard to using off-label treatments which lack clearly proven results but would be remiss in not availing patients to treatments offering real hope of improving their odds of survival.

On a personal note, the author is a physician specializing in allergy and asthma who became interested in this subject after being diagnosed with stage 4 pancreatic cancer in July 2016. At the time of diagnosis, the author had tumors in the head and the tail with scattered peritoneal metastases and a CA19-9 of 11,575 U/mL. Working with physicians from Weill-Cornell and Johns Hopkins

universities, the author began treatment with chemotherapy, plus intravenous (IV) paricalcitol (25 µg 3×/week) and oral hydroxychloroquine (600 µg BID). The author has now enjoyed a complete response with the latest CA19-9 of 15 U/mL and no evidence of active disease on the most recent CT scan. Although it is only a study of one, this response occurs no >1% of the time with chemotherapy alone. In a large-scale study of 340 stage 4 pancreatic cancer patients comparing gemcitabine to FOLFIRINOX, only one patient achieved a complete response.¹ Whether or not the author’s response was indeed due to the use of these off-label, complementary treatments, he understands the desire of patients to improve their odds, especially with therapies that have shown results in laboratory studies, retrospective studies, and animal models. Box 1 provides a list of human studies looking at the off-label agents in the treatment of pancreatic cancer.

Box 1 Human studies of agents for treatment of pancreatic cancer

Vit D

Pilot study: Paricalcitol for 1 month prior to resection (n = 12) → Increase T cell penetration into the tumor.⁹

HCQ

Phase II: HCQ without chemo (n = 20) → 2/20 (10%) had no progression at 2 months. Results insignificant.²²

Phase II: HCQ + pre-op SCRT + Gem (n = 50) → HCQ did not meaningfully impact survival.²³

Phase II: HCQ + chemo (n = 57) → More tumor destroyed, CA19-9 decreased, lower ratio of positive lymph nodes, greater apoptosis, less stromal activation, greater infiltration of CD4 and CD8 T cells, and increased PD-L1.²⁴

Vit C

Phase I: IV Vit C + Gem (n = 9) → Extended patients’ OS to 12 months vs. historical OS of 5.65 months.⁵⁶

Phase I: IV Vit C + Gem and erlotinib (n = 9) → 7 of 9 subjects had stable disease while only 2 had progressive disease.⁵⁷

Metformin

Retro: Mt in DM with resectable PC (n = 19)/control (n = 25) → 5-Year survival rates of 34% vs. 14%.⁷²

Retro: Mt (n = 117)/control (n = 185) DM with PC → 2-Year survival rate was 30.1% vs. 15.4%. OS was 15.2 months vs. 11.1 months. Statistical significance only in patients with nonmetastatic disease.⁷³

Phase II: Mt + Gem and erlotinib (n = 60)/control (n = 61) in advanced metastatic disease → No difference in OS.⁷⁴

Phase II: Mt + PEXG (n = 31)/control (n = 30) in advanced disease → No difference in OS.⁷⁵

Retro: Mt (n = 336)/control (n = 644) → OS of 9.9 months vs. 8.9 months. Statistical significance only in the locally advanced PC group.⁷⁶

Statins

Retro: Simvastatin (n = 680)/atorvastatin (n = 149)/control (n = 1,747) → 31% and 39% decrease in mortality.⁸⁵

Retro: Statin (n = 118)/control (n = 1,643) → 5-Year survival of 16.6% vs. 8.9% for nonusers. Simvastatin showed the greatest benefit.⁷⁹

Retro: Simvastatin with resectable PC (n = 71)/control (n = 155) → Improved OS.⁸⁶

Retro: Statin use after diagnosis (n = 2,456)/control (n = 5,357) → Improved OS in patients with grade 1/2 tumors with resection, but not in patients with higher-grade tumors.⁸⁷

Phase II: Simvastatin + Gem 40 mg (n = 57) in stage 4 PC/control (n = 57) → No significant difference in time to progression.⁸⁹

Retro: Statins + erlotinib and Gem for unresectable PC (n = 17)/control (n = 163) → Improved OS of 8.1 months vs. 3.9 months.⁹⁰

Metformin/statin

Retro: PC patients (n = 12,572) → Statin use improved OS; Mt use did not improve OS.⁷⁷

Curcumin

Phase II: Curcumin 8 g/d daily without chemo (n = 21) → 1 patient remained stable for >18 months and another patient had a dramatic but brief tumor response. Curcumin downregulated expression of NF-κB, COX-2, and other markers.¹²⁷

Phase I/II: Curcumin 8 g/d + Gem in Gem-resistant PC patients (n = 21) → Well tolerated with OS of 161 days (too small for analysis).¹²⁸

Aspirin

No studies for PC treatment; only prevention.

Abbreviations: Vit D, vitamin D; HCQ, hydroxychloroquine; chemo, chemotherapy; pre-op SCRT, preoperative short-course chemoradiation; Gem, gemcitabine; Vit C, vitamin C; IV, intravenous; OS, overall survival; Retro, retrospective study; Mt, metformin; DM, diabetes mellitus; PEXG, cisplatin, epirubicin, capecitabine, and gemcitabine; PC, pancreatic cancer.

Methods

The relevant medical and scientific English literature was reviewed using PubMed, Google Scholar, and ClinicalTrials.gov. To be included in this review, treatments were required to meet the following criteria:

1. Have shown positive results in multiple studies using pancreatic cancer cell lines and animal studies.
2. Have completed at least Phase I trials in humans and are advancing to Phase II trials and/or have large retrospective studies supporting their use.
3. Are available to the general public who are willing to utilize off-label treatments if prescribed by a physician, without enrolling in a clinical trial.

Vitamin D

Vitamin D deficiency and cancer

Vitamin D deficiency appears common in most cancer patients. One study found that 75% of cancer patients had low vitamin D levels. In this study, low serum vitamin D levels predicted advanced-stage disease. In fact, in patients with levels under 24 ng/mL, the risk of stage 3 disease was almost triple that of those with higher vitamin D levels.²

In another study, cancer patients had a significantly lower mean serum vitamin D level (24.9 ng/mL) relative to a cohort of noncancer primary care patients (30.6 ng/mL, $P < 0.001$).³

In regard to pancreatic cancer, in a study looking at 2 large US cohorts totaling 122,198 people of whom 365 developed pancreatic cancer, higher dietary intake of foods containing vitamin D was associated with a lower risk for pancreatic cancer.⁴

In a pooled analysis of 5 prospective cohorts with 451 cases and 1,167 controls, higher plasma levels of vitamin D were associated with a lower risk for pancreatic cancer ($P = 0.005$).⁵

Paricalcitol, a synthetic analog of vitamin D

Paricalcitol is a modified form of vitamin D that acts as a vitamin D receptor agonist and is not associated with systemic toxicity of vitamin D resulting in conditions such as hypercalcemia. It is currently available intravenously or orally to treat or prevent hyperparathyroidism in dialysis patients.

Recently, investigators at the Salk Institute for Biological Studies have found that paricalcitol helps break through the pancreatic tumor's stroma, which acts as a protective shield, incasing the tumor. The stroma is part of an extracellular matrix obstructing the tumor's vasculature and inhibiting

chemotherapy delivery to the tumor site. Specifically, the pancreatic stellate cells (those surrounding the tumor cells) are particularly activated in pancreatic cancer, driving the production of the stroma, as shown in Figure 1. These stellate cells have high levels of vitamin D receptors, and the blocking of these receptors by paricalcitol inactivates the stromal production.⁶ These stellate cells also produce cytokines and growth factors that enhance local tumor growth, contribute to angiogenesis, and enable metastasis. Furthermore, stellate cells metastasize along with the cancer cells assisting in their seeding, survival, and proliferation.⁷

In mice, when paricalcitol was given along with gemcitabine, stromal activation and tumor size were both significantly reduced, resulting in a 57% prolongation of survival.⁷

In addition to stromal inactivation, vitamin D has been shown to exert antiproliferative effects, secondary to the upregulation of the cell cycle inhibitors, especially p21 and p27, which control cell proliferation, differentiation, and division.⁸ Studies have shown a reduction of several pancreatic tumor lines in mice treated with paricalcitol correlating with the degree of cell cycle kinase inhibition.⁸

Lastly, paricalcitol has been shown to increase T cell penetration into the tumor. In a small Phase I study in patients treated with paricalcitol for 1 month prior to tumor resection, a 10- to 100-fold increase in the number of T cells was observed in and around the tumor.⁹ The hope that vitamin D affects the tumor's immune environment has inspired the start of a Phase II study combining paricalcitol with immunotherapy and chemotherapy.¹⁰

Vitamin D may have many other anticancer effects, as well, not limited to pancreatic cancer. Evidence suggests that vitamin D promotes apoptosis leading to quicker cancer cell death.¹¹ This has been evaluated in other cancers such as retinoblastoma.¹² Vitamin D has been shown to inhibit angiogenesis within tumors.¹³ Tumors cannot grow larger than a few millimeters or metastasize unless they are well vascularized.

Safety of paricalcitol

In terms of safety, as stated, paricalcitol is less likely to produce hypercalcemia, hyperphosphatemia, or elevations in calcium and phosphorus levels compared to other forms of vitamin D, primarily due to its decreased effect on intestinal absorption of calcium and phosphorus.¹⁴

In a Phase I dose-escalating trial of IV paricalcitol in men with advanced prostate cancer, patients received as much as 25 μg 3 \times /week intravenously. Significant hypercalcemia was rare, and the maximally tolerated dose of paricalcitol was not

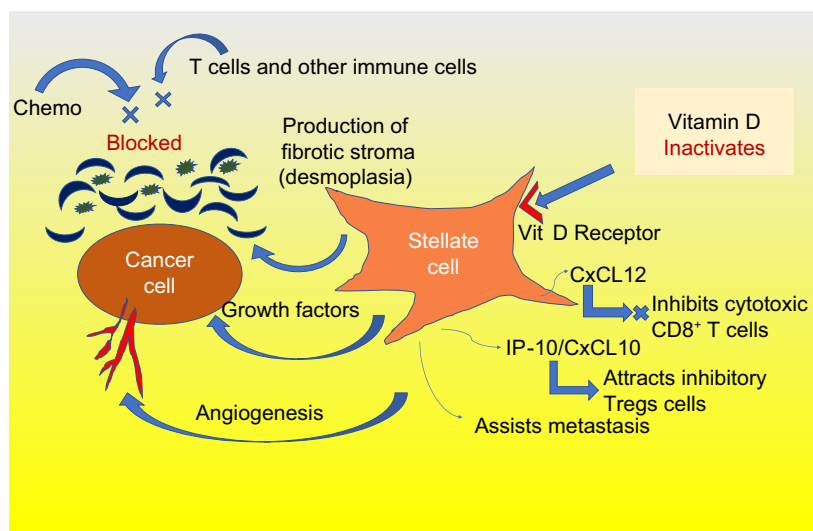


Figure 1 Stellate cells are overactive in pancreatic cancer and are inactivated by vitamin D.

Abbreviation: Vit D, vitamin D.

reached in that study, indicating that even higher doses may be free of significant side effects.¹⁵ Paricalcitol has also been shown to be well tolerated in mice at relatively high levels.

In summary, paricalcitol given intravenously at a dose of 25 µg, 3×/week, appears to be well tolerated with little risk of serious adverse side effects in humans. It has worked well in vitro and in vivo (mouse studies) indicating possible benefit in combination with chemotherapy in human pancreatic cancer. Large-scale studies in humans are just beginning.

Hydroxychloroquine

Hydroxychloroquine is a relatively inexpensive drug currently available for the treatment of malaria, lupus, and rheumatoid arthritis. It is currently in clinical trials, combined with chemotherapy, for the treatment of pancreatic and other cancers.

Hydroxychloroquine has been shown to inhibit autophagy. Autophagy is a process of self-cannibalization in which injured cancer cells ingest pieces of themselves, such as organelles and macromolecules, to conserve energy, and, therefore, thrive. Additionally, autophagy helps rid the cancer cells of toxic substances and free radicals, such as hydrogen peroxide and superoxide. When combining chemotherapy with autophagy inhibition, damaged cancer cells are unable to conserve the needed energy to survive.

How autophagy works

First, the structures within the cells including toxic substances, free radicals, and damaged organelles that are no longer needed are targeted for removal. They are engulfed by a double-membrane structure that elongates and wraps

around them to form an autophagosome. The autophagosome then fuses with a lysosome, leading to the degradation and removal of the enveloped structures. This process, as shown in Figure 2, creates energy to replenish other critical cell functions necessary for cancer cell survival.¹⁶ In addition to creating energy, autophagy acts to remove toxic substances that may be damaging to the cell.¹⁷ Drugs such as chloroquine, and the less toxic, hydroxychloroquine, inhibit the last step in the process, preventing the lysosome from clearing the undesirable substances contained in the autophagosome.¹⁸

Why is autophagy important in pancreatic cancer?

The KRAS genetic mutation, found in over 90% of pancreatic tumors, appears to upregulate the process of autophagy which may be responsible for the extreme resilience of pancreatic cancer cells.¹⁹ When the KRAS oncogene was introduced into mice, it enhanced autophagy, which lead to faster growing, more aggressive tumors.²⁰ Because of this transformation, pancreatic cancer, more so than other cancers, appears to have a distinct dependence on autophagy, with studies showing increased autophagic activity occurring within these cancer cells.²¹ The rapidly dividing cells within tumors require more energy than normal cells to reproduce. When chemotherapy agents attack the pancreatic cancer cells, their ability to conserve energy, through autophagy, becomes especially critical.

Studies of pancreatic cancer cells in laboratories have shown that inhibition of autophagy makes survival of cancer cells more difficult by such processes as increasing reactive oxygen toxins, elevating DNA damage, and causing a meta-

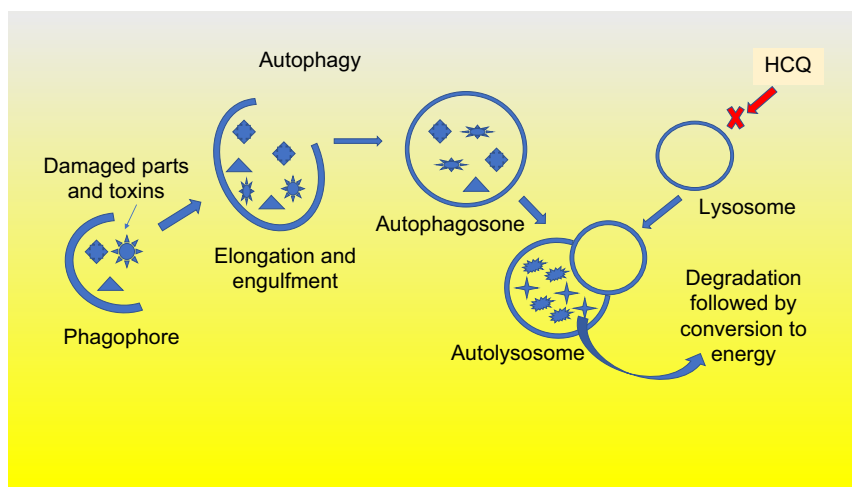


Figure 2 Autophagy is activated by KRAS mutation. The process of autophagy is highly active in pancreatic cancer cells and clears the damaged cancer cells of toxins and dying organelles to create the needed energy to survive and divide. Hydroxychloroquine prevents this autophagy process.

Abbreviation: HCQ, hydroxychloroquine.

bolic defect leading to decreased mitochondrial oxidative phosphorylation.²¹

In mice studies, decreased autophagy has led to robust tumor regression and prolonged survival of the mice. In a 16-mouse xenograft study, the response to chloroquine was dramatic. Of the 8 mice treated with chloroquine, 7 (88%) survived over 180 days, compared to all 8 untreated mice dying within 140 days.²¹ Additional studies in mice with genetic pancreatic tumors also showed promising results.

Human studies

One human study using hydroxychloroquine alone (without chemotherapy) produced disappointing results with only 2 of 20 patients without progressive disease.²² In another negative study of 50 patients on hydroxychloroquine 800 mg daily plus preoperative short-course chemoradiation and gemcitabine, disease-free survival did not significantly improve.²³ On the bright side, an interim report of an ongoing Phase II study showed encouraging results. This study which analyzed 54 patients with resectable or borderline resectable pancreatic cancer receiving hydroxychloroquine 1,200 mg daily, in addition to chemotherapy, showed that the percentage of tumor destroyed was better in the hydroxychloroquine group ($P = 0.004$). Additionally, the CA19-9 tumor marker in patients receiving hydroxychloroquine decreased by 20%, as compared to 10% in the chemotherapy-alone group ($P = 0.014$), and at the time of surgery, the ratio of positive lymph nodes to total number of lymph nodes was lower in the hydroxychloroquine group vs. the control group (0.03 vs. 0.05; $P = 0.02$). The hydroxychloroquine group had greater apoptosis in

their tumors, less stromal activation, and greater infiltration of CD4 and CD8 T cells ($P = 0.016$ and $P = 0.046$, respectively), and greater tumor expression of PD-L1. No adverse effects were noted in this study.²⁴

Risks associated with hydroxychloroquine

The major risk associated with hydroxychloroquine is retinopathy, potentially leading to blindness. At the typical dose of 200 mg 2×/day (for autoimmune diseases), the risk is exceedingly small with <2% of patients developing retinopathy after 20 years.²⁵ The higher doses being tested to prevent autophagy (800–1,200 mg daily dosages are currently in clinical trials) carry a higher risk. Two small studies have shown some degree of retinal damage occurring in under 2 years.²⁶ Therefore, at high doses, screening by an ophthalmologist is recommended every 6 months, as early detection is the only method to prevent serious retinal damage.

IV vitamin C

Evidence that vitamin C (ascorbic acid) is beneficial in prolonging life in cancer patients dates back to the 1970s.^{27,28} However, while some studies on oral vitamin C have shown success in breast cancer,^{29,30} most studies in other cancers failed to show any success with oral administration.^{31,32} Evidence suggests the high blood concentrations required to induce cytotoxicity can only be achieved with IV administration.³³ IV vitamin C should be avoided in patients with G6PD deficiency due to a risk of hemolysis, but otherwise appears extremely well tolerated in almost all patients.

When vitamin C is given orally, plasma levels peak at 100 μM . With greater oral doses, absorption decreases while urine excretion increases, so that blood levels cannot rise. In contrast, when vitamin C is administered intravenously, plasma concentrations of 1 mM or higher can be achieved without toxicity.^{33–36}

Vitamin C is believed to work because it breaks down into hydrogen peroxide, which is especially toxic to catalase-deficient cancer cells. Healthy noncancerous cells produce enough catalase to protect themselves from the toxic effects of hydrogen peroxide, resulting in no adverse effects to them.^{37–39} For example, in one study, there was an increase in measured hydrogen peroxide production that correlated with concentrations of vitamin C. Cell death by vitamin C was reversed when scavengers of hydrogen peroxide were added to cell lines.³⁸ In another study, when 11 human cancer cell lines were exposed to serial dilutions of vitamin C, a correlation between catalase activity and the susceptibility to ascorbic acid was observed.⁴⁰

Another theory on the effect of vitamin C in the treatment of cancer suggests that its toxicity is due to an increased uptake of its oxidized form, dehydroascorbate (DHA), via the GLUT1 glucose transporter that is upregulated in KRAS- and BRAF-mutated cells. Increased DHA uptake is believed to cause an oxidative stress by depleting glutathione and inactivating glyceraldehyde phosphate dehydrogenase, resulting in an energetic crisis and cell death. This was studied in colorectal cancer cells with these mutations, and hopefully, also applies to pancreatic cancer cells, of which >90% contain the same KRAS mutation. In that study, vitamin C treatment inhibited KRAS- and BRAF-mutant cell growth and colony formation much greater than in their nonmutant counterparts. In the same study, vitamin C treatment significantly reduced tumor growth compared to vehicle control treatment in mice bearing established cancer xenografts.⁴¹

It is likely that both theories are correct. As one study showed, adding catalase, which neutralizes hydrogen peroxide, to cell lines treated with vitamin C reversed 75% of the effect but not all of it.³⁹ Additionally, studies have shown that both cell lines with low catalase activity^{37,40,42} and cell lines expressing the KRAS mutation^{38,41,43} are much more sensitive to vitamin C.

IV vitamin C may also cause a metabolic defect in the difficult-to-kill pancreatic cancer stem cells (CSCs). These are the cells most resistant to chemotherapy and are responsible for recurrence of cancer even after the metastatic cells have been destroyed. These stem cells rely on oxidative phosphorylation (OXPHOS) as their primary energy source,

as opposed to glycolysis. A recent study showed that vitamin C can be used to target the stem cell population, as it is an inhibitor of energy metabolism that feeds into the mitochondrial tricarboxylic acid cycle and OXPHOS.⁴⁴

Studies in cancer cell lines

In laboratory studies, vitamin C has proven to be potently cytotoxic to a wide variety of cancer cell lines^{45–53} including pancreatic cancer.^{38,47} Additionally, it has been shown to boost the cytotoxicity of several common chemotherapy drugs.^{37,41,54}

Mice studies

In vitro studies have been further confirmed in animal studies, where IV vitamin C decreased the growth rates of liver, ovarian, pancreatic, and glioblastoma tumors with dosages easily achievable in humans.⁵⁵

In a study looking at 7 different pancreatic cell lines, gemcitabine–vitamin C combinations administered to mice bearing pancreatic tumor xenografts consistently enhanced inhibition of growth compared to gemcitabine alone. Growth inhibition of 50% more than gemcitabine alone was seen, and vitamin C administration demonstrated a gemcitabine dose-sparing effect.³⁹

In mice treated with vitamin C, a slower rate of growth in pancreatic tumors was observed in comparison to the control group of animals that received NaCl. On day 21 of the experiment, the control group had a mean tumor volume of 472 mm^3 , while the vitamin C group had a mean tumor volume of 138 mm^3 . Additionally, mice that received vitamin C had increased survival compared to controls (68 days vs. 78 days; $P < 0.0001$).³⁸

Human studies

The primary goal of Phase I studies is to evaluate safety and determine dosing, although some small insight into efficacy can be ascertained.

A small Phase I clinical trial in the USA has just shown that adding IV vitamin C to gemcitabine for pancreatic cancer extended patients' average survival time to 12 months, compared to historical survival times of 5.65 months for such patients.⁵⁶

In another Phase I study of IV vitamin C in combination with gemcitabine and erlotinib, 7 of 9 subjects had stable disease while only 2 had progressive disease.⁵⁷

Neither of these studies showed any significant toxicity. Larger Phase II studies are just beginning.

Combinations of off-label treatments with vitamin C

Almost no research in mice or humans has been done combining different off-label treatments. Theoretically, some combinations may be synergistic. For example, IV vitamin C increases the free radical hydrogen peroxide within cancer cells. This triggers autophagy,^{38,58} presumably to detoxify the cells. Adding hydroxychloroquine that inhibits autophagy would make it more difficult to clear the hydrogen peroxide, leading to quicker cell death.

Lastly, metformin and vitamin C may be synergistic as they both have been shown to block OXPHOS in the pancreatic stem cells.

Metformin

The diabetic drug, metformin, seems to have an effect of inhibiting pancreatic CSCs, but not metastatic cancer cells. Therefore, it may be useful in cancer prevention, in early-stage disease, and in prevention of recurrence after remission, although it is likely not helpful in metastatic disease.

How it works

Pancreatic CSCs are dependent on mitochondrial oxidative metabolism for their energy requirements, whereas metastatic cells rely on glycolysis.⁵⁹ Glycolysis breaks down glucose and forms pyruvate with the production of 2 molecules of ATP. Alternatively, in mitochondrial oxidative metabolism, glucose plus oxygen leads to CO₂ production and a plethora of ATP. Metformin inhibits the mitochondria, and thereby, shuts down oxidative metabolism in the stem cells resulting in an energy crisis leading to apoptosis. Because metformin decreases mitochondrial respiration, cells treated with metformin become energetically inefficient. Inhibition of mitochondrial oxidative metabolism in CSCs has been shown to significantly decrease their survival.⁶⁰ Unfortunately, in at least one study, the stem cells eventually adapted by changing their metabolic process and became metformin resistant.⁵⁷

A second effect of metformin is indirect inhibition of mammalian target of rapamycin. In pancreatic cancer, the mTOR pathway functions downstream of RAS, and therefore, is in part activated by the KRAS mutation. Activation of this pathway correlates significantly with a poor prognosis.⁶¹ MTORC1, the primary regulator of the mTOR pathway, stimulates ribosome biogenesis and transcription of genes, leading to cell growth, division, and differentiation primarily within stem cells.

A third effect metformin has is to reduce desmoplasia, similar to that seen with vitamin D. This occurs by inhibiting

the activation of the pancreatic stellate cells that produce the extracellular matrix and by reprogramming immune cells to reduce inflammation. For metformin, this effect is primarily seen in diabetic and obese patients.^{62,63}

Lastly, evidence suggests that metformin inhibits proliferation, migration, and invasion of drug-resistant pancreatic cancer cells by attenuating CSC function by deregulation of certain microRNAs (miRNAs). miRNAs are small noncoding RNAs involved in the modulation of several biological activities ranging from invasion to metastases development, as well as drug resistance in pancreatic cancer.⁶⁴

Mice studies

In a xenograft mouse model, low doses of metformin inhibited cellular transformation and selectively killed CSCs in 4 genetically different types of breast cancer.⁶⁵

In a study on the effects of metformin on pancreatic intraepithelial neoplasia (PanIN) and its progression to pancreatic cancer in mice, 2 doses of metformin decreased pancreatic tumor weights by 34% and 49%, respectively ($P < 0.03$ – 0.001). The drug treatment caused suppression of PanIN3 (carcinoma in situ) lesions by 28% and 39%, respectively ($P < 0.002$), and significant inhibition of carcinoma spread in the pancreas. The CSC markers were significantly decreased ($P < 0.04$ – 0.0002) in the pancreatic tissue. This study implied that the biologic effects of metformin are mediated through decreased CSC markers CD44 and CD133, CSC markers and modulation of the mTOR signaling pathway.⁶⁶

In another study of hamsters fed a high-fat diet, 50% of the hamsters not given metformin developed malignant lesions, compared to none in the metformin group ($P < 0.05$). The non-metformin group also developed significantly more hyperplastic and premalignant lesions, most of which were found within the islets, (8.6 lesions/hamster) than in the metformin group (1.8 lesions/hamster).⁶⁷

In a third study, metformin given orally to mice inhibited MaiPaca-2 implanted xenografts by 67% and markedly reduced the growth of preestablished PANC-1 xenografts in a dose-dependent manner. A decrease in MTORC1 and extracellular-signal-regulated kinase signaling in the metformin-treated xenografts was also demonstrated.⁶⁸

In another study comparing metformin and rapamycin, both significantly reduced tumor burden compared with vehicle, although the effect of rapamycin was more dramatic. Additionally, both metformin and rapamycin significantly decreased tumoral mTOR activity.⁶⁹

Prevention of pancreatic cancer in humans

In a retrospective cohort study of 62,809 diabetics treated in the UK, metformin monotherapy carried the lowest risk of cancer. Metformin use was associated with lower risk of cancer of the colon or pancreas, although it did not affect the risk of breast or prostate cancer.⁷⁰

In another hospital-based case-control study at MD Anderson Cancer Center performed over 4 years, diabetic patients who had taken metformin had a significantly lower risk of pancreatic cancer compared with those who had not taken metformin ($P = 0.001$). In contrast, diabetic patients who had taken insulin or insulin secretagogues had a significantly higher risk of pancreatic cancer compared with diabetic patients who had not taken these drugs. This study demonstrates that metformin use was associated with reduced risk and insulin or insulin secretagogue use was associated with increased risk of pancreatic cancer in diabetic patients.⁷¹

Positive human studies in pancreatic cancer

Two recent small studies showed improved survival in early-stage disease. A recent small Phase II study of 44 patients showed trend toward improved survival with the use of metformin in diabetic patients with resectable pancreatic cancer. The median overall survival of 10.4 months was longer in those who took metformin than in those who did not. Furthermore, the long-term survival was higher in the metformin group than in the control group, with 5-year survival rates of 34% and 14%, respectively. Due to the small size of this study, the results did not reach statistical significance.⁷²

In another retrospective study of 302 diabetic patients with pancreatic cancer, the 2-year survival rate was 30.1% for the metformin group and 15.4% for the non-metformin group ($P = 0.004$). The median overall survival time was 15.2 months for the metformin group, and 11.1 months for the non-metformin group ($P = 0.004$). The beneficial effect of metformin was seen in all disease stages but reached statistical significance only in patients with nonmetastatic disease.⁷³

Negative studies in humans with metastatic disease

Unfortunately, metformin has not been shown to be effective in 2 Phase II studies of 60 and 121 patients with metastatic disease.^{74,75}

In a retrospective study of 980 diabetic patients on metformin with pancreatic cancer, the findings failed to show

any benefit in metastatic disease and showed only a small protective effect in patients with locally advanced disease.⁷⁶

A Surveillance, Epidemiology, and End Results (SEER) data analysis of 12,572 Medicare patients with pancreatic cancer, exposed to statins but not metformin, showed that use of statins alone was significantly associated with reduced overall mortality and the combination of the 2 was not superior to statins use alone.⁷⁷

Statins

Several large-scale retrospective studies of pancreatic patients taking statins show impressive results in reducing mortality, especially in early-stage disease. Evidence also shows statins help prevent pancreatic and various other types of cancers. Hydrophobic/lipophilic statins (atorvastatin, simvastatin, lovastatin, fluvastatin) are likely more effective than hydrophilic statins (pravastatin and rosuvastatin) in cancer treatment since they are able to cross biological membranes, and therefore, have greater intracellular access.⁷⁸

Antitumor effects by statins

Cancer cells require increased lipid biosynthesis to meet their metabolic needs and supply cholesterol to the cell membrane.⁷⁸ The inhibition of cholesterol production, however, plays only a small role in the effect statins have on cancer cells. More importantly, statins, through inhibition of HMG-CoA reductase, inhibit not only cholesterol formation but also the entire mevalonate pathway. In addition to cholesterol, this pathway also leads to the production of isoprenoids, dolichol, ubiquinone, and isopentenyl adenine. Several members of this pathway have been shown to be essential for the survival of several cancer cell lines. Inhibiting the production of these factors leads to a decrease in cancer cell growth, protein synthesis, and cell cycle progression and to an increase in apoptosis in many cancer types. These effects appear to be independent of cholesterol, and in fact, studies have not shown a correlation between cholesterol levels and cancer progression. Two other products of the mevalonate pathway, farnesyl pyrophosphate and geranylgeranyl pyrophosphate, are required to activate the RAS protein, and their inhibition has been shown to increase cell apoptosis.⁷⁹

Studies with pitavastatin in pancreatic cell lines revealed dose-dependent growth inhibition. At the molecular level, pitavastatin induced expression of the cyclin-dependent kinase inhibitor p21 in a cholesterol-independent manner.⁸⁰

A recent study revealed a significant increase in survival of mice with pancreatic cancer fed atorvastatin ($171.9 \pm$

6.2 days) compared to the control mice (144.9 ± 8.4 days; $P < 0.05$). Atorvastatin treatment resulted in a significant reduction in tumor volume and cell proliferation. Atorvastatin also inhibited several key proteins, including KRAS protein, and their activities.⁸¹

Statins in prevention of pancreatic cancer

In a meta-analysis of 18 studies that included 1,799,157 patients, the incidence of pancreatic cancer was 0.28% in the statin therapy group vs. 0.54% in the group without statin therapy.⁸²

In a study of over 500,000 veterans, statin use of >6 months was associated with a risk reduction of pancreatic cancer of 67%. An impressive 80% risk reduction was found with use of a statin for >4 years.⁸³

While several studies showed a decreased risk of pancreatic cancer among statin users, several studies looking at all cancers showed an increased risk of cancer, especially in the elderly. This pro-cancer effect is thought to be due to a stimulatory effect on Treg cells.⁸⁴

Retrospective studies in pancreatic cancer patients

A study of 2,427 pancreatic cancer patients, of whom 680 were taking simvastatin and 149 were taking atorvastatin, demonstrated a 31% decrease in mortality in the group taking Zocor (simvastatin) and a 39% decrease in the group taking Lipitor (atorvastatin).⁸⁵

In another study among the 1,761 pancreatic cancer patients of whom 118 had used statins, the 5-year overall survival was 16.6% for statin users and 8.9% for nonusers ($P = 0.012$). Simvastatin showed the greatest benefit.⁷⁹

Among 226 patients undergoing resection for pancreatic cancer, 71 (31.4%) had prior simvastatin use and 27 (11.9%) had prior lovastatin use. Active use of moderate- to high-dose simvastatin at baseline was associated with improved overall and disease-free survival.⁸⁶

A study of 7,813 elderly patients with pancreatic cancer showed statin treatment after cancer diagnosis was associated with enhanced survival in patients with low-grade, resectable pancreatic cancer.⁸⁷

A 14-year study showed that statin use at the time of any cancer diagnosis was associated with 15% reduced cancer-related mortality in Danish patients.⁸⁸

As previously mentioned, a SEER data analysis of 12,572 Medicare patients with pancreatic cancer, exposed to statins but not metformin, showed that statin use was significantly

associated with reduced overall mortality, especially in post-diagnosis statin users.⁷⁷

Mixed studies in metastatic disease

Unfortunately, a double-blind prospective study of 114 stage 4 patients failed to show any benefit from simvastatin 40 mg.⁸⁹

Another study with 180 patients treated with erlotinib–gemcitabine for unresectable pancreatic cancer showed that a history of statin treatment resulted in improved overall survival ($P = 0.026$).⁹⁰

Curcumin

Curcumin is the most studied of the nutraceuticals that are considered anticancer agents found in natural plants. Agents such as epigallocatechin-3-gallate from green tea have been shown in vitro to induce apoptosis and inhibit tumor progression by modulating different signaling pathways in pancreatic cancer.^{91,92} Others, such as isoflavone from soybeans, resveratrol from grapes, lycopene which is the red pigment in tomatoes, and garcinol from the rind of the fruit, have shown promise in the laboratories but may be limiting due to lack of absorption and bioavailability. Nutraceuticals are also believed to work by affecting the expression of certain miRNAs which modulate cellular signaling networks leading to the inhibition of pancreatic cancer cell growth and pancreatic CSC self-renewal.^{93,94}

Curcumin, from the plant *Curcuma longa* and a component of turmeric, has exhibited multiple anticancer effects in numerous studies in pancreatic cell lines and mice studies.^{95–114} When used in combination, curcumin has also been shown to potentiate the effects of other cytotoxic agents, including gemcitabine, cisplatin, oxaliplatin, and 5-fluorouracil, in preclinical models of a variety of cancers.^{96,105} Most importantly, it seems to prevent chemoresistance especially to gemcitabine.^{102,104–109}

A low incidence of cancer has been documented in countries that incorporate high consumption of turmeric root, of which curcumin is believed to be the active ingredient.^{110,111} After testing >1,000 different potential agents for cancer prevention, the National Cancer Institute has chosen only 40, of which curcumin was included, to be moved to clinical trials.¹¹² In several mice studies, curcumin has been shown to prevent cancer including mammary adenocarcinoma, esophageal cancer, and familial adenomatous polyposis.^{113–115}

Disappointingly, its low bioavailability limits its effectiveness. To improve the bioavailability of curcumin, numerous approaches have been undertaken, including the formation

of liposomes, micelles, and phospholipid complexes, as well as attempting different routes of administration such as subcutaneous dose of microparticles, intraperitoneal delivery, and IV administration.¹¹⁶

Fortunately, new formulations including the nanoparticles of curcumin have been recently investigated. One such product, with the brand name Theracurmin[®], is currently available and appears to provide significantly greater blood levels and greater hopes of efficacy. Other preparations are also under development.

How curcumin works

Curcumin has demonstrated a plethora of functions affecting various cell signaling pathways at multiple levels, as shown in Figure 3. Studies have identified numerous factors inhibited by curcumin related to cancer cell survival, proliferation, invasion, angiogenesis, and metastasis, suppression of apoptosis, and chemoresistance. Curcumin has been shown to inhibit a variety of factors including STAT3,¹⁰⁰ COX-2,¹¹⁷ survivin,¹⁰⁰ miR-200, and miR-21,¹¹¹ the hedgehog pathway,¹¹⁸ and IAP proteins.¹¹⁹ Additionally, it has been demonstrated to activate the cell cycle inhibitors, p27 and p21,⁹⁴ and upregulate the p53 modulator of apoptosis.¹¹² Curcumin has been shown to inhibit pancreatic tumor growth and angiogenesis in mouse models.¹²⁰

Curcumin's most important effect seems to stem from inhibition of the transcription factor NF- κ B and all its downstream products.^{96,97,110,117,118} Many lines of evidence suggest that NF- κ B plays a major role in growth, proliferation, angiogenesis, and most importantly, chemoresistance.^{104–106,117,121} Becoming resistant to chemotherapy is the main cause of death in most pancreatic

patients. Curcumin seems to block this resistance.¹²² For example, one study showed that resistance to gemcitabine is induced by NF- κ B activity and that curcumin inhibits this process.¹⁰⁷ A recent study demonstrated curcumin restores sensitivity in gemcitabine-resistant cancer cells and confirmed this finding in a xenograft mouse model.¹⁰⁸

Nanoparticles

Unfortunately, the bioavailability of curcumin is very low. The most likely explanation of its low plasma and tissue levels appears to be poor absorption, rapid metabolism, and rapid systemic elimination.¹²³ Multiple studies report plasma levels of curcumin rarely exceed 40 ng/mL even with extremely high oral intake including amounts over 8 g.^{124–126} Therefore, Phase I and II human studies with curcumin have demonstrated good tolerability, albeit with only limited effectiveness.^{127,128}

In order to increase bioavailability, there have been several attempts to create different formulations, the most successful of which have been nanoparticles.^{95,122} Nanoparticles of curcumin are formed by encapsulation in polymeric micelles, liposomes, or hydrogels, all of which make these particles water-soluble, and therefore, easily absorbable. One such nanoparticle formulation has shown a much greater bioavailability in several studies^{129,130} including a >40-fold increase in area under the blood concentration–time curve compared with conventional curcumin in rat models and a 27-fold increase in a human trial.¹³¹ In another study, the maximal plasma curcumin concentration of Theracurmin was 10.7–5.6 times higher than 2 other curcumin preparations also claiming a novel drug-delivery system.¹³² Small human studies have shown an

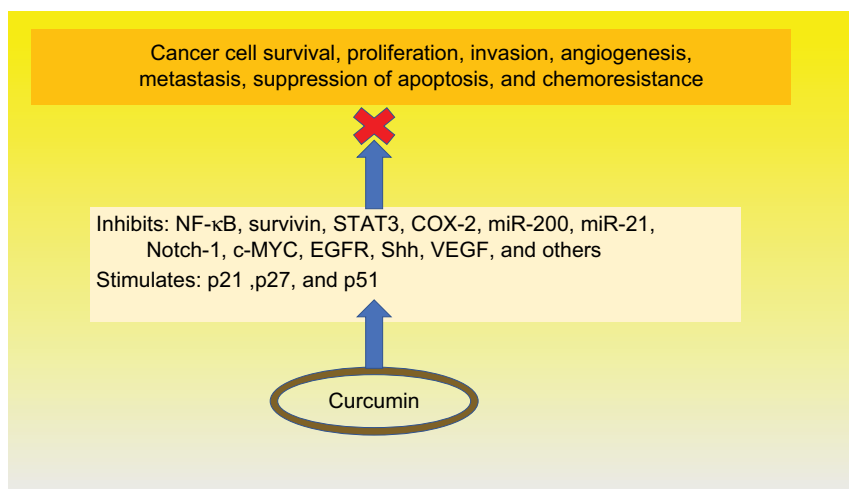


Figure 3 Functions of curcumin.

Abbreviations: NF- κ B, nuclear factor kappa enhancer of activated B cells; STAT3, signal transducer and activator of transcription 3; COX-2, cyclooxygenase 2; miR, microRNAs; Notch-1, neurogenic locus notch homolog protein-1; c-MYC, c-myc proto-oncogene; EGFR, epidermal growth factor receptor; shh, sonic hedgehog; VEGF, vascular endothelial growth factor; P21, p27 and p51, cyclin-dependent kinase inhibitors.

excellent safety profile with good tolerability,^{129,130} although there are only limited data on efficacy. Larger-scale studies have yet to be performed.

Aspirin

Aspirin may be useful in pancreatic cancer prevention as indicated in several large retrospective studies. Many pancreatic cancer patients are greatly concerned about family members as pancreatic cancer appears to have a genetic tendency, even when no known oncogenes such as BRCA are detected. We have already reviewed statins, metformin, and curcumin, all of which have shown some evidence in terms of cancer prevention.

Additionally, many patients who have undergone surgery or complete chemotherapy and are now cancer-free are not receiving any medications or treatment to prevent recurrence despite a high recurrence rate in these patients. Prevention of recurrence after surgery is an intriguing possibility, although it has yet to be studied in pancreatic cancer. Two studies, however, one in colon cancer and one in breast cancer, have shown prevention of recurrence with the use of aspirin.^{133,134}

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have shown promise in prevention of a variety of other cancers.¹³⁵ The greatest evidence has been seen with colorectal cancer, both in observational epidemiological studies^{136–139} and in prospective clinical trials.^{139,140} There is also evidence for a prophylactic effect for several other types of cancers, including stomach cancer,¹⁴⁰ esophageal cancer,¹⁴¹ leukemia,¹⁴² breast cancer,^{143,144} ovarian cancer,¹⁴⁵ endometrial cancer,¹⁴⁶ and prostate cancer.^{147,148}

Four studies have shown aspirin likely helps in pancreatic cancer prevention. The first is a population-based study performed during 2006–2011 in Shanghai, People's Republic of China, with 761 pancreatic cancer patients and 794 control subjects who were matched on sex and age. The results were rather impressive, demonstrating that regular use of aspirin reduced the risk of pancreatic cancer by almost half.¹⁴⁹

A population-based Connecticut study, conducted from January 2005 to August 2009, of 362 pancreatic cancer cases matched to 690 randomly sampled controls, showed that subjects who regularly used aspirin had a lower risk of pancreatic cancer. The more years of aspirin use, the greater the benefit.¹⁵⁰

In another prospective study from 1992 through 1999, among 28,283 postmenopausal women who lived in Iowa, of whom 80 developed pancreatic cancer, there was a trend of decreasing risk of pancreatic cancer with aspirin use, but not with nonsteroidal anti-inflammatory medications.¹⁵¹

Lastly, the Mayo Clinic performed a clinic-based case–control study from April 2004 to September 2010, evaluating the association between aspirin, NSAID, and acetaminophen use with pancreatic cancer risk using a sample of 904 patients with pancreatic cancer, and 1,224 age- and sex-matched healthy controls. They found that aspirin use, but not NSAID or acetaminophen use, was associated with a lowered risk of developing pancreatic cancer.¹⁵²

Unfortunately, not all studies show a reduced risk. In a study of 408 pancreatic cancer patients and 816 matched controls, overall statin use, but not aspirin use, was associated with a reduced pancreatic cancer risk. The authors of the study suggest that prior positive results for aspirin use may have resulted from concomitant statin use as many cardiovascular patients take both.¹⁵³

Studies of aspirin for treatment of pancreatic cancer have not yet been performed. A recent systematic review and meta-analysis of 58 mostly observational studies of various cancers, but not including pancreatic cancer, showed reductions in metastatic spread and a decrease in overall mortality by about 15%.¹⁵⁴

Although the mechanism by which aspirin prevents cancer is unknown, studies indicate it may be due to aspirin's ability to inhibit platelet upregulation of c-MYC which stimulates cancer cell proliferation. This has been demonstrated in both colon and pancreatic cancer cell lines.^{155,156} Evidence suggests the anticancer effect of aspirin relates to its ability to reduce metastasis possibly through its effect on platelets.¹⁵⁷ It has also been suggested that aspirin may work by inhibiting survivin, a protein which inhibits apoptosis and is overexpressed in pancreatic cancer.¹⁵⁸

Final thoughts

Given the dismal 7% overall survival rate in pancreatic cancer, with only 1% for stage 4, almost all patients are desperately seeking alternative options. Patients seeking the above-mentioned treatments should go to their oncologists armed with this paper and other medical publications rather than resorting to alternative or holistic providers who may not practice evidence-based medicine. Oncologists, therefore, must be prepared to assist patients in finding the most scientifically sound therapeutic options, lest they turn to the extremes of unconventional therapies, or even worse, to the counsel of charlatans.

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