Pancreatic Cancer alternate treatments

Conventional cancer treatments include surgery and various types of radiation therapy and chemotherapy. Apart from surgery, standard treatments do not prolong survival significantly. However, adjuvant systemic chemotherapy using gemcitabine showed some survival benefit in stage IV pancreatic cancer patients. The respective survival rates of the gemcitabine and surgery-only groups were 86 percent and 70 percent at one year, and 50 percent and 12 percent at two years, with a median survival time of 20 months and 14 months. The disease-free interval was improved, and the occurrence of hepatic metastasis was reduced in the gemcitabine group compared to the surgery-only group.

Long-Term Survival with Alpha-Lipoic Acid (Intravenous), Multiple Antioxidants, and Low-Dose Naltrexone

A recent case report describes the long-term survival (>3 years) of a 46-year-old man who was diagnosed with a very aggressive cancer of the pancreas (adenocarcinoma) which had spread to the liver (Berkson BM et al 2006). The patient had a 3.9 x 3.9 cm tumor in the head of the pancreas and 4 tumors in the liver, one of which was 5 to 6 cm in diameter. He was told there was not much that could be done for him, yet he was treated with one round of a typical chemotherapy regimen (Gemzar (gemcitabine) and Paraplatin (carboplatin)), which caused reduced blood cell counts but no tumor regression. He received a second opinion that any further treatment would be in vain, so he opted for an integrative medical approach (via the Integrative Medical Center of New Mexico).

For his non-cancer medical conditions he was given several antacids (Prevacid 30 mg, Rolaids), antibiotics (Primsol/Gantanol), anti-ulcer agents (Mylanta, Pepto-Bismol), and the anti-anxiety drug, Xanax, and then he started an integrative therapy program, the ALA-LDN (Intravenous Alpha-Lipoic Acid- Low-Dose Naltrexone) protocol.

The ALA-LDN protocol comprised alpha-lipoic acid (ALA) (300 to 600 mg intravenously twice weekly), low-dose naltrexone (Vivitrol) (3 to 4.5 mg at bedtime), and orally, ALA (300 mg twice daily), selenium (200 micrograms twice daily), silymarin (300 mg four times daily), and vitamin B complex (3 high-dose capsules daily). In addition, he maintained a strict dietary regimen, performed a stress-reduction and exercise program, and led a healthy lifestyle. Remarkably, after just one treatment of intravenous ALA his symptoms began to disappear, his quality of life improved, and he had no unwanted side effects.

His pancreatic cancer has remained stable for more than 3-years and he is free from symptoms. Several other patients are being treated with this protocol and, to date, with success (Berkson BM et al 2006). Thus, the ALA-LDN protocol could possibly extend the lives of those pancreatic cancer patients who have been led to believe that their cancer is terminal.

Alpha-lipoic acid is a potent antioxidant (Baraboi VA 2005), improves immune cells' functions (Mantovani G et al 2000), increases homocysteine levels in cancer cells which is toxic to them (Hultberg B 2003), and prevents the activation of nuclear factor kappaB (NF-kappaB) a key regulator of tumor development and progression (Sokoloski JA et al 1997; Suzuki YJ et al 1992;Vermeulen L et al. 2006). Selenium is useful in elevating antioxidant levels (Woutersen RA et al 1999; Zhan CD et al 2004) and silymarin is a selective COX-2 inhibitor (Cuendet M et al 2000a).

Low-dose naltrexone blocks opiate receptors causing the body to make large amounts of opiates in response, which in turn improve the immune response; specifically, natural killer cell cytotoxicity, B-cell and T-cell proliferation, and IFN-gamma production are maintained during times of immune suppression (Nelson CJ et al 2000).

Prevacid is an antacid that also improves cell-mediated immunity, prevents immune suppression, and may also exert anti-inflammatory

activity, all of which are important for cancer patients with impaired immune systems (Dattilo M et al 1998; Peddicord TE et al 1999).

Pancreatic Enzyme Replacement Therapy

Dr. John Beard, who published The Enzyme Theory of Cancer in 1911, was the first to propose using pancreatic digestive enzymes to treat cancer. Later, Dr. William Donald Kelley treated his cancer patients with enzymes for more than 20 years, and many lived far beyond expectations. By comparison, in a trial of 126 pancreatic cancer patients treated with the drug Gemzar, not one patient lived longer than 19 months (Burris HA3 1996). Treating patients with pancreatic extract containing enzymes resulted in significantly improved absorption in those with moderate-to-severe fat or protein malabsorption (Perez MM et al 1983).

In a remarkable study by Dr. Nicholas Gonzalez, 11 patients with pancreatic cancer were treated with large doses of pancreatic enzymes, nutritional supplements, 'detoxification' procedures, and an organic diet. Of the 11 patients, nine survived for one year, five survived two years, and four survived three years. This pilot study suggests that aggressive nutritional therapy with large doses of pancreatic enzymes significantly increased survival over what would normally be expected for patients with inoperable pancreatic cancer (Gonzalez NJ et al 1999). An experimental animal study found that treating tumors in mice with pancreatic enzyme extract (PPE) significantly prolonged their survival and slowed tumor growth (Saruc M et al 2004).

As a result of the pilot study, the National Cancer Institute and the National Center for Complementary and Alternative Medicine approved funding for a large-scale phase III clinical trial comparing Dr. Gonzalez's nutritional regimen against Gemzar in treating inoperable pancreatic cancer. This study has full FDA approval and is being conducted under the Department of Surgical Oncology at New York Presbyterian Hospital, Columbia Campus.

- "In the nutritional arm: Patients receive pancreatic enzymes orally every four hours and at meals daily on days 1-16, followed by five days of rest. Patients receive magnesium citrate and Papaya Plus with the pancreatic enzymes. Additionally, patients receive nutritional supplementation with vitamins, minerals, trace elements, and animal glandular products four times per day on days 1-16, followed by five days of rest. Courses repeat every 21 days. Patients consume a moderate vegetarian metabolizer diet during the course of therapy, which excludes red meat, poultry, and white sugar. Coffee enemas are performed twice a day, along with skin brushing daily, skin cleansing once a week with castor oil during the first six months of therapy, and a salt-and-soda bath each week. Patients also undergo a complete liver flush and a clean sweep and purge on a rotating basis each month during the five days of rest."

Several factors contribute to the effectiveness of pancreatic enzyme replacement therapy.

These include:

- Patient compliance and adherence to scheduled dose and timing of intake.
- Individual weight perception versus actual weight measurement.
- Type of pancreatic enzyme preparations, that is, pancrelipase powder versus enteric-coated products (Schibli S et al 2002). Delayed-release preparations (capsules containing enteric-coated microspheres, such as Creon) are reportedly less susceptible to acid inactivation in the stomach and duodenum, as they are designed to disintegrate at a relatively high gastrointestinal pH (greater than 5.5 to 6). Antacids or a histamine H2-receptor antagonist (cimetidine, Tagamet) have been used to decrease the inactivation of enzyme activity.

COX-2 (Cyclooxygenase-2) Inhibitors

The COX-2 enzyme is elevated in pancreatic cancer (Tucker ON et al 1999) and indirectly prevents cancer cells from dying (Chu J et al 2003). The COX-2 inhibitor Celebrex reduces levels of the COX-2 enzyme and is now being investigated for use in cancer treatment (Ferrari V et al 2005; Fosslien E 2000; Lipton A et al 2004).

The combination of Celebrex and 5-FU by prolonged intravenous injection was well tolerated and capable of producing long-lasting, measurable responses, even in patients with advanced pancreatic cancer (Milella M et al 2004). Selective reduction of COX-2 levels improves response to both chemotherapy and radiotherapy without being toxic to normal healthy tissues (Ferrari V et al 2005; Lipton A et al 2004). COX-2 inhibition sensitizes tumor cells to death by radiation and is now being studied in clinical trials (Rich TA et al 2004). However, COX-2 inhibitors may cause heart attack or stroke, as well as kidney damage. Because of these concerns, the FDA-approved drugs Vioxx and Bextra have been taken off the market by their manufacturers. Celebrex, however, is still available.

Suppressing the COX-2 enzyme may inhibit pancreatic cancer cell propagation. In the past, COX-2 inhibitors such as Celebrex (100-200 mg taken every 12 hours) were considered. However, with recent observations that people taking COX-2 inhibitors for prolonged periods have a higher incidence of cardiac and vascular problems, some of these drugs may no longer be available in the future. Instead, bioflavonoids could be considered at a dose of 250-1800 mg a day, or silymarin (420 mg/day) (Boari C et al 1981; Pares A et al 1998) and/or curcumin (3600 mg/day), which have demonstrated the ability to naturally suppress COX-2 (Gescher A 2004).

5-LOX (5-Lipoxygenase) Inhibitors

The 5-LOX enzyme is produced in pancreatic cancer (but not in normal pancreatic ducts) and is critical for its growth (Hennig R et al 2002). Reducing levels of 5-LOX prevents human pancreatic cancer

cell lines from multiplying and induces apoptosis (cell death). In a phase II study, the 5-LOX inhibitor CV6504 was well tolerated and maintained stable disease. The predicted one-year survival time was approximately 25 percent (Ferry DR et al 2000).

Zileuton, a 5-LOX inhibitor, was approved in the United States in September 2005 for the prevention and chronic treatment of asthma in patients 12 years and older. The drug is contraindicated in patients with active liver disease.

Nutritional intervention aims to:

- Reduce the occurrence of pancreatic cancer.
- Decrease treatment-related disease and deaths.
- Improve long-term survival via direct therapeutic effects.

Consuming a diet rich in fruit and vegetables, along with controlling calories by dietary measures or exercise, will help to prevent pancreatic cancer (Lowenfels AB et al 2004). A constituent of cruciferous vegetables such as watercress called phenethyl isothiocyanate (PEITC) stopped pancreatic cancer from developing in a hamster model that was given a cancer-causing agent (a carcinogen known as BOP) (Nishikawa A et al 2004).

*Monoterpenes***.** Monoterpenes are found in the essential oils of citrus fruits and other plants. The monoterpenes limonene and perillyl alcohol demonstrate intense antitumor activity against pancreatic cancer cells (Crowell PL et al 1996; Gelb MH et al 1995). They counter cancer by:

- Jump-starting enzymes that are able to break down cancer-causing chemicals.
- Preventing cancer cell growth by reducing ras activity and causing cancer cell death.
- Restraining liver enzyme actions (hepatic HMG-CoA reductase activity), which controls cholesterol production and thus cancer cell growth.

Limonene. Found in citrus fruits, limonene reduces the growth of pancreatic cancer cells by 50 percent (Karlson J et al 1996). The tentative dose recommendation for limonene is 7.3 to 14.4 grams per day (Boik J 2001; Igimi H et al 1976; Vigushin DM et al 1998). According to studies, limonene is well tolerated in cancer patients at doses that may have clinical activity (Salazar D et al 2002). One partial response in a breast cancer patient at a dose of 8 grams taken twice daily was maintained for 11 months, and three additional patients with colorectal cancer showed disease stabilization for longer than six months on d-limonene at 0.5 or 1 gram taken twice daily (Vigushin DM et al 1998).

Perillyl Alcohol. Perillyl alcohol is found in small concentrations in the essential oils of lavender, peppermint, spearmint, sage, cherries, cranberries, perilla, lemongrass, celery, and caraway seeds (Belanger JT 1998). Perillyl alcohol exhibits powerful effects in minimizing cancer cell growth (Hardcastle IR et al 1999; Stark MJ et al 1995) and preventing the mutated ras proteins from continuously stimulating cancer cell growth (Broitman SA et al 1995; Burke YD et al 2002).

- Twelve clinical trials have investigated the use of perillyl alcohol in various types of cancer treatments. A 2050-mg dose administered four times daily was found to be easily tolerated (Morgan-Meadows S et al 2003). In one clinical trial, perillyl alcohol was administered four times a day to 16 patients with advanced cancers not responding to treatment. Evidence of antitumor activity was seen in a patient with metastatic colorectal cancer who had an ongoing near-complete response of greater than two years' duration. Several patients had stable disease for as long as or greater than six months (Ripple GH et al 2000). The predominant toxicity of perillyl alcohol seen during most trials was gastrointestinal (nausea, vomiting, and belching), limiting the dose. The minimum required antitumor dose is 1.3 grams per day (Boik J 2001).

Gamma Linolenic Acid (GLA) a fatty acid found in borage oil slows the growth and spread of pancreatic cancer by hindering tumor blood-vessel development (Cai J et al 1999). GLA treatment changes tissue blood flow dramatically in pancreatic tumors, even at low doses (Kairemo KJ et al 1998; Ravichandran D et al 1998).

Intravenous administration of the lithium salt of GLA (Li-GLA) to 48 patients with inoperable pancreatic cancer was associated with longer survival times (Fearon KC et al 1996).

A cell-culture study investigated possible interactions between GLA and 5-FU or Gemzar. GLA had a synergistic effect with Gemzar at concentrations that correspond to therapeutic doses in the body. However, GLA with 5-FU was synergistic only within a tight range of high concentrations of 5-FU (Whitehouse PA et al 2003).

Fish Oil. Patients with advanced pancreatic cancer usually experience weight loss (catabolic wasting or cachexia) and often fail to gain weight with conventional nutritional support. EPA, an essential fatty acid found in fish oil, restrains pancreatic cancer cell growth in laboratory experiments at low doses and decreases the number of cancer cells at higher doses (Lai PB et al 1996). The maximum tolerated daily dose of fish oil was found to be 0.3 grams per kilogram (kg) of body weight. This means that a 70-kg (154-lb.) patient can generally tolerate up to 21 grams of fish oil containing 13.1 grams of EPA and DHA (Burns CP et al 1999). However, in a phase I study of five pancreatic cancer cachexia patients, a mean dose of approximately 18 grams per day (doses ranged from 9 to 27 grams per day) of a new high-purity preparation of EPA as a 20 percent oil and water diester emulsion was tolerated (Barber MD et al 2001).

Several studies have shown that supplementation with fish oils containing EPA and DHA is helpful and may even reverse weight loss caused by cancer (Merendino N et al 2003; Wigmore SJ et al 2000). Moreover, consumption of a protein- and energy-dense oral nutritional supplement containing omega-3 fatty acids (such as EPA)

improves body weight, lean body mass, and quality of life in patients undergoing chemotherapy (Bauer JD et al 2004; Chen da W et al 2005; Klek S et al 2005).

Fish oil supplements providing at least 2400 mg of EPA and 1800 mg of DHA daily have been recommended (Anderson KM et al 1998a). To reduce cachexia, an estimated 2 to 12 grams per day of EPA is needed (Gogos CA et al 1998; Persson C et al 2005; Rosenstein ED et al 2003; Thies F et al 2001).

Clinical Studies: Fish Oil and Pancreatic Cancer

Many clinical studies have shown that fish oil supplementation stabilizes the rate of weight loss, as well as adipose tissue and muscle mass, in pancreatic cancer patients, who often suffer from wasting (Tisdale MJ 1999).

- Protein supplements enriched with EPA increased total energy expenditure and physical activity levels in advanced pancreatic cancer patients, thereby increasing their quality of life (Klek S et al 2005; Moses AW et al 2004).
- Twenty pancreatic cancer patients were asked to consume two cans of a fish oil-enriched nutritional supplement daily in addition to their normal food intake. Each can contained 16.1 grams of protein and 1.09 grams of EPA. At the study's onset, all patients were losing weight at a median rate of 2.9 kg a month. After administration of the fish oil-enriched supplement, patients had a significant weight gain at both three and seven weeks (Barber MD et al 1999).
- In another study, after three weeks of consuming an EPA-enriched supplement, the body weight of cancer patients had increased, and their energy expenditure in response to feeding had risen significantly to levels no

different from baseline healthy control values (Barber MD et al 2000).

In a study of 18 pancreatic cancer patients who supplemented with fish oil capsules (1 gram each containing EPA 18 percent and DHA 12 percent), patients had a median weight loss of 2.9 kg a month before supplementation; three months after beginning fish oil supplementation, patients had a median weight gain of 0.3 kg a month (Wigmore SJ et al 1996).

Food-Derived Polyphenols

Genistein prevents pancreatic cancer cell growth primarily by regulating sugar metabolism (Boros LG et al 2001). In addition, genistein inactivates NF-kappa B (Li Y et al 2005), thus sensitizing cancer cells to chemotherapeutic agents such as Gemzar (Banerjee S et al 2005), cisplatin and docetaxel (Li Y et al 2004), and VP-16 and doxorubicin (Sato T et al 2003). In laboratory experiments, genistein has been shown to improve survival, reduce tumor blood-vessel development (Buchler P et al 2004), almost completely inhibit cancer metastasis, and increase cancer cell suicide (Buchler P et al 2003).

If the pathology report shows that the pancreatic cancer cells have a mutated p53 oncogene, or if there is no p53 detected, then high-dose genistein therapy may be appropriate (Choi YH et al 2000; Wilson LC et al 2003). If the pathology report shows a functional p53, then genistein is less effective in stopping cancer growth. The suggested dose of genistein is approximately 500 mg daily (Miltyk W et al 2003; Takimoto CH et al 2003).

Green Tea is particularly rich in polyphenols such as epigallocatechin gallate (EGCG) that act as antioxidants. Black and green tea extracts reduce pancreatic tumor cell growth by approximately 90 percent while preventing angiogenesis (Maiti TK et al 2003; Masamune A et al 2005; Roomi MW et al 2005). They also decrease the expression of the K-ras gene (Lyn-Cook BD et al 1999a) and the invasiveness of pancreatic cancer cells (Takada M et al 2002). Animal experiments of

pancreatic cancer show that tea polyphenols restrain carcinogen-induced increases in oxidative DNA damage (Frei B et al 2003).

Green tea extract curbs the process of pancreatic cancer development (Lyn-Cook BD et al 1999b) and the promotion of transplanted human pancreatic cancer in animals, and also causes pancreatic cancer cell death (Hiura A et al 1997; Qanungo S et al 2005).

In humans, an inverse relationship was observed between the amount of green tea consumed and the risk of developing pancreatic cancer; the highest intake was associated with the lowest risk of cancer (Ji BT et al 1997). In clinical studies, green tea supplementation has been shown to be safe and protective (Ahn WS et al 2003; Chow HH et al 2001; Chow HH et al 2003).

Antioxidants. Free radicals can cause repeated damage to normal cells and reduce the function of injured tissues. When sufficient antioxidants are available, free radicals are removed before excess damage occurs. Antioxidant levels are reduced in pancreatic cancer compared to other pancreatic diseases and healthy pancreatic tissue, resulting in increases in reactive oxygen (Cullen JJ et al 2003) that are capable of stimulating cancer cell division (Garcea G et al 2005; Vaquero EC et al 2004).

Increased levels of some antioxidants may be useful in slowing the growth of pancreatic cancer (Weydert C et al 2003). Vitamins A, C, and E, as well as selenium, increase antioxidants in the body needed to reduce free-radical damage (Woutersen RA et al 1999).

Vitamins A, C, and E. In animals in which pancreatic cancer was caused by chemicals, cancer incidence was decreased by 64.3 percent by vitamin A and by 71.4 percent with vitamin C. Both vitamins increased SOD (superoxide dismutase) activity and were toxic to tumor cells but not to normal healthy cells (Wenger FA et al 2001).

- An overview of 14 randomized trials (with a total of 170,525 patients) showed significant effects of supplementation with

beta-carotene, vitamins A, C, E, and selenium (alone or in combination) versus placebo on pancreatic cancer incidence (Bjelakovic G et al 2004).

- A study of 23 pancreatic cancer patients tested retinol palmitate (vitamin A) and beta-interferon with chemotherapy. Eight patients responded and eight patients had stable disease. For all patients, median time to disease progression and survival time were 6.1 months and 11 months, respectively. Toxicity was high, but patients who had responses and disease stabilization had prolonged symptom relief (Recchia F et al 1998).
- Retinoids curb the growth and adhesion of a variety of pancreatic cancer types, even those that previously have been documented to be resistant to retinoids (El-Metwally TH et al 1999). Vitamin E succinate restrained pancreatic cancer cell growth in laboratory experiments (Heisler T et al 2000).
- Ascorbyl stearate, a fat-soluble form of ascorbic acid (vitamin C), markedly restrained the growth of—and even killed—pancreatic cancer cells (Naidu KA et al 2003).

Selenium. Selenium and beta-carotene were found to restrain the growth of pancreatic tumors caused by carcinogen exposure in mice (Appel MJ et al 1996). Selenium levels were found to be reduced in pancreatic cancer patients who underwent surgery to remove the upper portion of their intestine (Armstrong T et al 2002). In preclinical studies, a diet high in selenium reduced the number of carcinogen-induced pancreatic cancers significantly (Kise Y et al 1990).

Curcumin has many anticancer effects. It is a selective inhibitor of the COX-2 enzyme and may be beneficial in preventing and treating pancreatic cancer (Cuendet M et al 2000). It decreases NF-kappa B activity, which is involved in controlling the growth of pancreatic cancer cells (Li L et al 2004). It also inhibits interleukin-8 (IL-8) production, which affects invasiveness, cell growth, and tumor blood-vessel development (Hidaka H et al 2002).

PSK (Polysaccharide K) is a protein-bound polysaccharide derived from the mycelium of the mushroom Coriolus versicolor (Tsukagoshi S et al 1984). In Japan, PSK is used as a non-specific biological response modifier to enhance the immune system in cancer patients (Koda K et al 2003; Noguchi K et al 1995; Yokoe T et al 1997). PSK suppresses tumor cell invasiveness by down-regulating several invasion-related factors (Zhang H et al 2000). Also, PSK can enhance pancreatic cancer cell death induced by Taxotere (docetaxel) (Zhang H et al 2003).

Two patients who had unresectable pancreatic cancer were treated with combined chemotherapy using cisplatin, PSK, and UFT (uracil-tegafur). During therapy, a partial response was observed, with a remarkable decrease in tumor size and no significant side effects. From the results of these two cases, this combination chemotherapy was considered to be one of the most effective therapies available for pancreatic cancer (Sohma M et al 1987). PSK has been used as adjuvant immunotherapy for cancer at a dose of 3 grams daily (Ito K et al 2004; Ohwada S et al 2004; Toge T et al 2000).

Ukrain (NSC-631570) a semi-synthetic agent has been used in complementary medicine for more than 20 years to treat benign and malignant tumors. In a phase II trial of advanced pancreatic cancer patients, Ukrain either alone or together with Gemzar(gemcitabine) was found to be well-tolerated with only moderate toxicity, and doubled median survival times (Gansauge F et al 2002). In another study, Ukrain improved the quality of life of patients suffering from advanced pancreatic cancer while significantly prolonging their survival time (Zemskov V et al 2002).