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Proteolytic Enzyme Therapy in Pancreatic Cancer Treatment: A Review

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ABSTRACT

The cancer of the pancreas has a poor diagnosis due to the location of the pancreas. It has a high mortality rate of about ninety five percent, with limited survival rate. Patients diagnosed of pancreatic cancer barely have five years to live. Pancreatic cancer cells, cancer cells in general, posses a tough fibrin coat which protects them from the body's own immune system and various types of chemotherapy have been unable to overcome this barrier. This is because the fibrin coat of cancer cells, resist fibrinolytic degradation by the fibrinolytic enzymes due to high cysteine residues in the fibrin protein. The use of proteolytic enzymes in pancreatic cancer treatment is aimed at degrading this fibrin coat, hence exposing the cancer cells to the body's own immune system. This therapy is also accompanied with some components such as diet, and detoxification procedure known as the coffee enema. Studies on cancer cells have shown that the issue of the body's autonomic system has to be addressed using diet. To avoid future diseases as a result of tumor degradation, the coffee enema is carried out so as to efficiently eliminate toxins through the liver.

Keywords: Pancreatic Cancer, Fibrin, Cancer Cells, Immune System Proteolytic Enzyme Therapy

INTRODUCTION

Cancer has proven to be one of the most devastating diseases known to mankind. Many cancer treatments have shown little or no curative effect with side effects sometimes more fatal than cancer cells itself. Pancreatic cancer is a type of cancer that originates from the pancreas. Pancreatic cancer cells are protected with a coat which is composed of fibrin and of a polymeric form of human serum albumin (HSA) which, by contrast to pure fibrin, is resistant to fibrinolytic degradation (Egyud *et al.*, 2005). Fibrin physiologically is a coagulating agent essential to good

health in that it stops bleeding. Cancer cells have a special way of converting fibrin into a sticky coat around its membrane. This sticky coating can be up to fifteen times thicker than the membrane of normal cells (Wrba *et al*, 2012), which is why various chemotherapy have found it difficult destroy cancer cells. The case is not the same when an enzyme is able to unveil the mask and hence the immunological system finds the cancer cells foreign to the body. There have been several clinical studies in a variety of cancers showing improvements in quality and prolongation of life with proteolytic enzyme supplementation (Leipner *et al*, 2000).

PANCREATIC CANCER

Pancreatic cancer is also called carcinoma of the pancreas or cancer of the pancreas. Worldwide, cancer of the pancreas is responsible for about five percent of cancer deaths every year. It is often referred to as the "silent disease" because symptoms are few and non-specific, leading to late diagnosis in the majority of cases (Ashraf *et al.*, 2010). Pancreatic cancer is the fourth most common cause of cancer-related deaths in the United States (Hariharan *et al.,* 2008). Pancreatic cancer has the highest mortality rate of all major cancers. Ninety four percent of pancreatic cancer patients will die within five years of diagnosis; only six percent will survive more than five years. Seventy four percent of patients die within the first year of diagnosis (American Cancer Society, 2011).

Due to the location of the pancreas, cancer may grow for some time before it causes symptoms (Ashraf *et al.*, 2010). Pancreatic Cancer cells can also break away from the primary (original) tumor and enter the bloodstream or the lymphatic system. They may invade and destroy the tissue around them. This process is the way cancer spreads to form new tumors in other parts of the body which are called metastases.

Types of Pancreatic Cancer

The American Cancer Society (2010) state that types of pancreatic cancer is based on the cell type and location of the tumor in the pancreas. The pancreatic cancer is classified into two, the endocrine and exocrine pancreatic cancer. Ninety-five percent of pancreatic cancers develop from the exocrine pancreas. The remaining five percent are often called neuroendocrine tumours or islet-cell cancers; these develop from the endocrine cells.

Exocrine Pancreatic Cancers

Exocrine cancer of the pancreas is the commonest type of pancreatic cancer; they start in the cells of the exocrine pancreas, which produces

the digestive pancreatic juices. There are a number of different types of exocrine pancreatic cancers and are as follows:

- **Adenocarcinoma:** This is cancer of the exocrine cells that line the pancreatic ducts. The majority of pancreatic cancers are this type.

- **Cystic Tumors:** Tumors that cause fluid filled sacs in the pancreas. Most are benign.

- **Acinar Cell Cancers:** Tumors that form on the ends of the pancreatic ducts in the cells that produce enzymes.

- **Sarcomas:** Tumors that form in the connective tissue that bonds together the pancreatic cells. This is very rare.

- **Ampullary Cancers:** Cancer that develops in the ampulla of vater (where pancreatic ducts and bile ducts merge).

Endocrine Pancreatic Cancer

Endocrine tumors are uncommon. They start in the endocrine pancreas, where insulin and other hormones are made and released directly into the bloodstream. They are also called neuroendocrine tumours or islet cell tumours. About a third of these tumours produce hormones, which can cause some strange symptoms. Most of these tumours are non cancerous (benign).

Causes and Risk Factors

Despite extensive studies, no definite cause for pancreatic cancer has been identified. There are, however, several identifiable risk factors include; Smoking (Ashraf *et al.*, 2010), diet high in red meat and animal fat, diabetes, chronic inflammation of the pancreas, occupational exposure to petroleum and certain chemicals.

Symptoms of Pancreatic Cancer

The location of the pancreas may lead to poor detection of the pancreatic cancer until it reaches its advanced stage. By the time symptoms occur, diagnosing pancreatic cancer is usually relatively straight forward. Unfortunately, a cure is rarely possible at that point (© Pancreatic Cancer Health Center). Pancreatic cancer symptoms frequently include; Abdominal pain, weight loss, itching, weakness (cancer of the islet-cell can cause the pancreas to produce and secrete too much insulin or other hormones which may lead to weakness), dizziness, jaundice (yellow skin), muscle spasms or diarrhea.

DIAGNOSIS OF PANCREATIC CANCER

Diagnosis of pancreatic cancer can be carried out as required by a physician using any of the methods as described by Ashraf and Donald (2010) below:

- **An Upper-GI Series:** (sometimes called a barium meal). This is a series of X-rays of the upper digestive system, taken after the patient has swallowed a barium solution. The barium shows an outline of the digestive organs on the X-rays.

- **A CT Scan:** This uses a computerised X-ray machine to show images of the internal organs. The patient lies on a bed which moves through a circular hole as the machine takes pictures. He or she may be asked to drink a special substance prior to the scan – this will show up the bowel more easily.

- **An MRI Scan:** This uses a powerful magnet linked to a computer. The MRI machine is very large, with space for the patient to lie in a tunnel inside the magnet. The machine measures the body's response to the magnetic field, and the computer uses this information to make detailed pictures of areas inside the body.

- **Ultrasonography:** This uses high-frequency sound waves that cannot be heard by humans. A small instrument sends sound waves into the patient's abdomen. These cannot be felt, but the echoes bounce off internal organs, creating a picture called a sonogram. Healthy tissues and tumours produce different echoes. This investigation is good for lean people, but fat tissue may distort the signal.

- **ERCP (Endoscopic Retrograde Cholangiopancreatography):** This is a method for taking X-rays of the common bile duct and pancreatic ducts. The doctor passes a long, flexible tube (endoscope) down the throat, through the stomach, and into the small intestine. Dye is then injected into the ducts and X-rays are taken. This procedure is usually done under sedation.

- **PTCA (Percutaneous Transluminal Coronary Angioplasty):** A thin needle is put into the liver through the skin on the right side of the abdomen. Dye is injected into the bile ducts in the liver, so

blockages can be seen on X-rays.

- **Angiography:** This involves injecting dye into blood vessels so that they show up on the X-rays.

  A biopsy of a suspicious lesion or washings of the ducts (done via ERCP) will provide a definitive diagnosis.

- **Blood Tests**: Blood test in the form of tumour markers may also be requested

Stages in Pancreatic Cancer

Pancreatic cancer is assessed using the T, N, M staging system. This system measures the size of the primary tumor (T), the involvement of regional lymph nodes (N), and the presence of distant metastases (M) respectively. It is very important to determine the extent of the cancer growth to assess the possibility of surgical removal. Larger pancreatic cancers are less likely to be treated by surgery due to a reduced likelihood of success (FreeLove *et al.*, 2006).

Based on the staging results, pancreatic cancers can be classified into one of four categories: resectable (these tumors may be removed surgically), borderline resectable, locally advanced unresectable and disseminated. This evaluation system is based on imaging results and allows the surgeon to judge the likelihood of success (National Comprehensive Cancer Network, 2007).

FIBRIN IN PANCREATIC CANCER CELLS

Cancer cells in recent times have been discovered to having some form of resistance to chemotherapy. This is possibly as a result of certain complex molecules present on the cellular membrane. Fibrin, which is a very vital insoluble molecule in clothing, has been discovered to be produced from fibrinogen by cancer cells and be used for protection against the body's own immunological system. The process stimulates the liver to produce more fibrinogen and make the bloodstream as a whole more sluggish and susceptible to clotting. Despite increased concentration of plasminogen activator (tPA) in malingnant tumours, fibrinolytic potential in blood of cancer patients and tumour tissues is low, hence histochemical and microscopic examination revealed the presence of fibrin like material coating tumour cells. But there is however, a confirmed observation of that thrombin generation is not accompanied with the formation of this fibrin like

material (Constantini *et al.*, 1991). The increased concentration of –SH groups and arginine rich peptides, and the activation of tissue transglutaminase in the tumour tissue are responsible for the resistance of fibrin coat to enzymatic degradation. Cancer cells also produce insoluble form of human serum albumin (HSA) which is associated with fibrinolytic inhibition (Soreide *et al.*, 1991). With the presence of certain conditions, a complex is formed between the insoluble human serum albumin (HSA) and fibrinogen through a disulfide exchange reaction (Lipinski, 1995). Such complex is mainly formed in the presence of free radicals such as hydroxyl which are generated in the presence of iron or copper (Lipinski *et al.* 1992). The fibrin coat complex, in turn, causes neoplastic cells not to be recognized by the immunological system and thus makes them immune to the attack by the natural killer cells (Egyud *et al.,* 1991). This cancer cell protein (Fibrin) coat also presents a negative electrical charge around the cell that hides and protects the diseased cell against the body's own (also negatively charged) T-blood cells that normally destroy foreign infectious agents and diseased cells, instead the cancer and T-blood cells repel one another due to "like charges repelling." (Wikianswer, 2012). On the basis of these findings, a concept was put forward according to which the reducing condition of the cancer environment causes the expression of extracellular cysteine residues (Skalska *et al.*, 2009) and generation of hydroxyl radicals that, in turn, catalyze the formation of insoluble fibrin-HSA complexes. Such complexes when deposited on the surfaces of cancer cells form a protease-resistant coat that is presented as "self" to the innate and/or extrinsic cellular immune systems. Therefore, the effectiveness of any form of therapy is determined by its ability to overcome this protective barrier.

THE ENZYME THERAPY

Enzymes are molecules that speed up chemical reactions, they either helps build new molecules or they split the bonds that join molecules together to break them into smaller units. Proteolytic enzyme therapy is a plan of dietary supplements of plant and animal proteolytic enzymes used to facilitate the digestive process and improve the body's ability to maintain balanced metabolism. The use of the proteolytic enzyme therapy in pancreatic cancer treatment has far been used by many physicians. Dr. H. Wrba describe his method as The Systemic Enzyme Therapy (Wrba, 2004), Dr. N. Gonzalez modified a method by Dr. W.D Kelly and it is called the Gonzalez Regiment (Gonzalez, 1999), which is more

complex in itself, it basically involves three components; large doses of proteolytic enzymes, along with diet, nutritional supplements, and "detoxification" procedures (Leipner *et al.*, 2000). For cancer patients, long experience has taught that it is not enough to load patients with enzymes; the question of autonomic imbalance must also be addressed. In terms of pancreatic patients specifically, a plant-based diet provides all the nutrients to correct autonomic dysfunction. So, by the careful use of diet, major changes in autonomic function, and bring about balance in a dysfunctional nervous system. It is found further, as the autonomic system comes into greater harmony and balance, when the autonomic branches are equally strong, all systems from the immune system to the cardiovascular system work better regardless of the underlying problem. In essence, diet is used to bring about greater physiological efficiency. Another important factor in cancer pathogenesis is iron overload known to contribute to the generation of the most biologically active hydroxyl radicals. Iron is contained in red meat and thus its excessive consumption may explain the positive association with advanced prostate cancer, as well as other forms of cancer (Boguslaw Lipinski, 2010)

The third component of the therapy involves what is called "detoxification" routines. "Detoxification" refers to procedures such as the coffee enema, which are believed by alternative practitioners to enhance liver function and in turn, the processing and excretion of metabolic wastes (Gonzalez, 2004).

The coffee enema is a procedure of inserting coffee into the anus to clean the rectum and large intestines (Ernst, 1997). This procedure, although is well documented is considered by most medical authorities to be unproven, rash and potentially dangerous (Shils *et al.*, 1982).

The coffee enema is used to detoxify the liver, not the colon. It is a low-volume enema that remains only in the sigmoid colon. There is a duct between the sigmoid colon and the liver called the "entero-hepatic circulation system". When the stool reaches this point, it contains many toxins, which are sent to the liver for detoxification (Gonzalez, 2012).

Without getting too technical, the caffeine that is absorbed into the entero-hepatic system causes the liver ducts, including the bile ducts, to empty into the sigmoid colon. Releasing the toxins in the liver

ducts makes room for toxins from the body to enter the liver for detoxification. The alkaloids in the caffeine stimulate the production of an enzyme called "glutathione-S-transferase", which is an enzyme that facilitates the liver detoxification pathways. The coffee enema is safe even for people who are sensitive to caffeine because the coffee remains in the sigmoid colon, where it will not be absorbed, provided the proper amount is used and the enema bag is not placed too high. (© 2002 Healing Daily).

The Proteolytic Enzymes

Proteolytic enzyme, also called Proteinase, are a group of enzymes such as Bromelain, chymotrypsin, trypsin, bromelain, rutin, papain, that break the long polypeptide chainlike molecules of proteins into shorter fragments and subsequently into their amino acids components (Encyclopedia Britannica, 2012**)**. Because the secretions from the stomach can destroy or inactivate proteolytic enzymes, tablets containing pancreatic enzymes are coated in such a manner so that the tablet does not break down until after it has passed through the stomach. This method is referred to as "enteric-coating." A study was carried out to investigate the mechanisms by which proteolytic enzymes such as trypsin, chymotrypsin, Papain and bromelain are able to cross the intestinal mucosal barrier after oral administration to man which suggests and also reported, but so far unexplained systemic absorption of proteolytic enzymes after oral administration in vivo may occur by self-enhanced Para-cellular transport. (Bock *et al.,* 1998). The proteolytic enzymes on absorption into the blood streams are selectively targeted at the cancerous cells and hence:

a) **Dissolves Fibrin- Cancer Cells:** The actions of bromelain, chymotrypsin, and trypsin play a vital role in this. They can break up the fibrin sheath concealing cancer cells. Bromelain is an aqueous extract of pineapple that contains a complex mixture of thiol proteases and non-protease components (Katya *et al*., 2009) which is most likely the reason for its ability to degrade the cancer fibrin coat. Proteases constitute the major components of bromelain and include stem bromelain (80%), fruit bromelain (10%), and ananain (5%). Among non-protease components are phosphatases, glucosidases, peroxidases, cellulases, glycoproteins and carbohydrates (Maurer, 2001). Bromalain preferentially cleaves Glycyl, Alanyl and Leucyl bonds of the fibrin molecule. This

then exposes the antigens on the cancerous cells membrane, hence the immune system is then more able to find and destroy them, and the overall levels of fibrinogen production fall to healthy levels. Eventually the macrophage ("Big Eater") engulfs and "eats" the cancer cell. Thousands of cells could be destroyed as a result of the above action.

b) **Boosting the Immune System:** The revealing of the antigens on the membrane of pancreatic cancer cells by the proteolytic enzymes lead to secretion of many cytokines particularly interferon and tumor necrosis factor a (TNF- a). Their actions help to cause apoptosis of the cancer cells. Bromalain has specifically been reported to induce cytokine production in human peripheral blood mononuclear cells (Barun, 2008).

CONCLUSION

Advances in enzyme therapy has shown that they are selectively cytotoxic to the cancerous cells and hence a better therapy in cancer treatment in that they do not interfere with normal body cells and their side effect is minimal. Enzyme therapy does not only provide treatment but also improve the body's defense mechanisms, enhances digestion and hence provides a healthier lifestyle. However, enzyme supplements have readily not been in wider use due to inadequate mechanisms to clinically support the enzyme therapy, but with improvement in research on this therapy, we so believe that enzymes will provide a lasting solution to cancer treatment and improved defense activity by the immune system.

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