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Nanocurcumin-Based Electrochemotherapy for Pancreatic Cancer: The Answer the World is Looking For

Raji Sundararajan* Professor

Electrical & Computer Engineering Technology, Purdue University, USA

The good news is that pancreatic cancer is relatively less common than many other cancers; it is the 12h most common cancer in the world along with kidney cancer, with 338,000 new cases in 2012 [1]. The bad news is that the survival rate is a pathetic 5-10%; this is due to lack of early detection and serious symptoms at the early stages and due to the drug resistance. The estimated 5-year prevalence of people in the world living with pancreatic cancer is 4.1 per 100, 000. It is highest in the Armenia (11.9/100,000) for men and highest in Czech Republic and Slovakia and Armenia for both men and women [1]. About 53% of pancreatic cancer occurred in more developed countries in 2012. The highest incidence is in the Europe and the North America; the lowest in Asia and Africa. In the US, an estimated 45,220 cases were diagnosed in 2013, and an estimated 38, 460 deaths [2]. Compare this with about 180-200,000 incidences of breast or prostate cancer, with 38-40,000 deaths. The drug response rate of the Cadillac drug for pancreatic cancer, the Gemcitabine is also a meagre 25%. A study of 21 pancreatic cell lines including Panc-1 showed the drug resistance of these cells to Gemcitabine. There are other research which investigate the Gemcitabine resistance in pancreatic cancer [3,4]. The 5-year survival rate of exocrine pancreatic cancer is 14%, 12%, 7%, 5%, 3% and 1% for stages IA, IB, IIA, IIB, III, and IV respectively; it is 61%, 52%, 41%, and 15% when treated with surgery for stages I, II, III, and IV respectively [5]. The various reasons/mechanisms for drug resistance that have been reported are [6,7]:

Cellular and Biochemical Mechanisms

- Decreased drug accumulation, due to decreased drug influx, increased drug efflux, and altered intracellular drug trafficking.
- Increased inactivation of drug or toxic intermediate;
- Increased repair or tolerance to drug-induced damage to DNA, protein, membranes, decreased drug activation, altered drug-targets, altered gene expression, and so on.

In vivo Mechanisms

- Pharmacological and anatomic drug barriers, host-drug interactions, including increased or decreased drug activation by normal tissues, relatively increased normal tissue drug sensitivity.

Thus, there is a critical need for alternate therapies and electrical-pulse-mediated chemotherapy, known as Electrochemotherapy (ECT) appears to be an ideal candidate for the uptake of Gemcitabine or any other promising drug. Application of appropriate voltage pulses at the correct frequency elicits both diagnostic and therapeutic responses in the cells, tissue and organ. Due to the application of voltages, charges are collected on the membrane which when exceeded the threshold level, renders the membrane permeable to external drug molecules, which otherwise are impermeable or poorly-permeable due to the membrane transport characteristics imposed by the hydrophilic/hydrophobic bilayer phopholipid bilayers of the cell plasma membranes. We obtained cell deaths in the range of 30s and 60s percent for Panc -1 cell line and in the high 60s% for Panc-28 cell line using two different electrical pulses; the first one with high intensity, low duration (microseconds) and the second one with low intensity and long duration (milliseconds). Same dosage of drug was used in all the cases. Considering that cell death was close to above 85% for the head and neck cancer cell using same dosage, the aggressiveness or the chemoresistance of the pancreatic cancer cell lines could be understood and seek alternate techniques to treat this lethal cancer.

Towards this, use of curcumin, the yellow pigment of the natural phytochemical, used for over 6000 years for its medicinal values, the Indian gold spice/herb turmeric is another excellent option. Although, curcumin is noted for its anti-cancer, anti-inflammatory, anti-oxidant, and anti-septic characteristics, it is not widely used for curing cancer due its limited bioavailability due to its rapid metabolic reactions. Encapsulating curcumin using polymeric nanopartciles, known as nanocurcumin and its efficacy on cancer cells are studied by both our group (on MCF-7 human breast carcinoma cells) and another group on pancreatic cells. In this study on eight pancreatic cell lines by Bisht et al. [8], they studied the effect of polymeric nanoparticle-encapsulated curcumin (nanocurcumin). The various pancreatic cancer cell lines studied include MIAPaCa, Su86.86, PL5, PL8, E3LZ10.7, BxPC3, Capan-1, and Panc-1. They were exposed to a 20x range of void polymeric nanoparticles (93-1852μg/mL). The size of the nanoparticles was 50nM. Viability study after 72 hours indicated no cytotoxicity to the cell lines. Unlike normal curcumin, nanocurcumin readily dispersed in aqueous media and it demonstrated comparable *in vitro* therapeutic efficacy compared to normal curcumin. Further, nanocurcumin's mechanisms of action on pancreatic ells are comparable to that of normal curcumin, including induction of cellular apoptosis, blockade of nuclear factor kappa B (NFκB) activation, and down regulation of steady state levels of multiple pro-inflammatory cytokines (IL-6, IL-8, and TNFα).

An addition, irreversible electroporation where-in use of a number of electrical pulses of various magnitudes and duration, without any drug is also conducted in several clinical trials with favourable results [9].

All these indicate that to control and/or cure the lethal pancreatic cancer, we need alternate therapies and electrical-pulse-mediated chemotherapy using gemcitabine and nanocurcumin and/or electrical pulses alone are possible candidates for further studies to transfer this technique from lab to the clinic.

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***Corresponding author:** Raji Sundararajan, Electrical & Computer Engineering Technology, Purdue University, USA, Tel: 765 494 6912; E-mail: raji@purdue.edu

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