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Pilot Therapeutic Protocol for the Treatment of Local Advanced Disease, such as the Generalized Peritoneal Carcinomatosis and for the Treatment of Distant Metastases in Human Malignant Neoplastic Disease – Targeting the Medium

Panagiotis Bouras*

[1]*Department of Pathology, University of Athens, Karterado, Santorini, Greece*

***Corresponding author: Panagiotis Bouras,** Department of Pathology, University of Athens, Karterado, Santorini, Greece, Tel: 00306972801054; E-mail: panbouras1@yahoo.gr

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Abstract

The phenomenon of life and the open thermodynamic systems in general may be described from the existence of i) a distinct separating border from the surrounding environment ii) specific structures inside it, which are functioning with some form of energy exchange with the environment and iii) the medium inside wherewith these functions are taking place. For living cells, this distinct border is the cell membrane, the structures are the cellular organelles and the medium is the cytoplasm (which is mainly consists of water). The research idea of this therapeutic protocol aims at the selective destruction of the "medium", namely the cytoplasm of the cancer cell, with concurrently preservation of the integrity of the cytoplasm of the nearby normal cells/tissues. This may be achieved with the gradual lowering of the core body temperature of the patient and concurrently introducing of a therapeutic solution of complementary, "anti-sense", polypeptides in the cancer cell, individually synthesized for every patient, accordingly to his malignancy type, with theoretically increasing of the freezing point of the malignant cell's cytoplasm, subsequent crystallization, expansion and rupture of its membrane at a temperature where the cytoplasm of the nearby healthy cells/tissues will remain intact.

Keywords: Local advanced disease; Peritoneal carcinomatosis; Distant metastases; Targeting the medium

Introduction

The phenomenon of life and the open thermodynamic systems in general may be overall described from the existence of i) a distinct separating border from the surrounding environment ii) specific structures inside them, which are functioning with some form of energy exchange with the environment and iii) the medium inside wherewith these functions are taking place. In the case of the cell, the distinct border is the cell membrane, the medium is the cytoplasm (which is mainly consists of water) with all the cellular organelles (mitochondria, lysosomes, endoplasmic reticulum, ribosomes, nucleus, etc.), where the entire basic cellular functions for the homeostasis and reproduction are taking place. Regarding cancer therapy, current pharmaceutical targets of the cancer cell are only concerning the border (cell membrane-receptors-monoclonal antibodies), the intracellular structures (DNA, microtubules) and the cellular functions that occur by these (cell cycle, reproduction).

Aim

The research idea of the specific pilot therapeutic protocol aims at the selective destruction of the "medium", namely the cytoplasm of the cancer cell with its crystallization and expansion at low temperature, the subsequent rupture of its cell membrane, with concurrently preservation of the integrity of the cytoplasm of the nearby normal cell/tissue.

Method

The above therapeutic target may be achieved with the gradual lowering of the core body temperature of the patient in the operating room in general anesthesia or cardioplegia and cardiopulmonary bypass or "reverse" Hyperthermic Intraperitoneal Chemotherapy "HIPEC" technique or submersion in cold fluid medium (e.g., water), with the concurrent introduction in the cancer cell of a therapeutic solution, individualized for every patient, based on the kind of its malignant neoplasia, so as to cause increase of the freezing point and subsequent crystallization of the cytoplasm of the cancer cell at higher temperature than that of the normal nearby cell/tissue. With the achievement of the crystallization of the cytoplasm of the cancer cell, the controllable cooling of the patient stops and the controllable rewarming of the body commences, so as in the place of cancer cells to have remained water due to their cell membrane rupture from crystallization and the subsequent melting of crystals from rewarming, while the structure of the normal cells, where there was no crystallization occur, will have been remained unaltered (water to water and dust to dust).

The aforementioned therapeutic solution will be created based on the tertiary molecular structure of the cancer proteins, which are overexpressed in the cancer cell or based on proteins, which are selectively expressed inside the cancer, but not in the normal, cell. These proteins will be identified during the operation by taking biopsy from the malignant neoplastic tissue and they will be precise identified through immunochemical staining and specialized molecular techniques. Therefore, as an immediate analysis of their tertiary structures (e.g., through crystallography X-ray diffraction technique

and Fourier transforms) and the subsequent identification of the amino acid sequence of the "malignant" polypeptides (e.g., through mass spectrometry). When the amino acid sequence is identified, it will be followed, with the use of the proteomic technology (e.g., Solid Phase Peptide Synthesizer-SPPS). The creation of a solution of enantiomeric, "anti-sense", polypeptides, theirs tertiary structures to be exactly complementary with the tertiary structure of the overexpressed proteins at the cytoplasm of the cancer cell, correspondingly with the precise symmetry seen among D- and L-enantiomers. The complementaries enantiomeric proteins could be created either with natural L-amino acids either with the use of D-enantiomeric amino acids from the expanded genetic code, either with the combination of both forms (L- & D-) amino acids. The synthesis technique of the enantiomerics polypeptides may be accomplished by following the reverse amino acid sequence of the natural polypeptides, fact that needs further research study.

With the introduction of the therapeutic solution of the "anti-sense" proteins in the cancer cell, a racemic solution of enantiomeric polypeptides in the cytoplasm will be created with the concurrently controllable lowering of body temperature of the patient with slow programmable freezing cryopreservation techniques. The crystallization of the racemic mixture will occur and subsequent of the cytoplasm, followed by its expansion and rupture of the cancer cell membrane. Concurrent the preservation of the normal tissues in their liquid phase will have also be achieved. Also, mixtures of cryoprotective solutions could be utilized, such as DMSO (Dimethyl-Sulfoxide) and glycerol or sugar trehalose, which are successfully used at the preservation of living tissues, so as in the cytoplasm of the normal cell to become vitrification and not crystallization. The crystallization, expansion and rupture of the cancer cell by the controllable lowering of the body temperature (0.5-1°C/min) could be theoretically assisted by the presence inside the cytoplasm of the cancer cell of larger amounts of carbon dioxide, produced by the the oxidative phosphorylation, due to the increased combustion and the higher metabolic turn over, as in correspondence with the easier crystallization and expansion of the beverages in the freezer than of the bottled water. This hypothesis is supported theoretically from the law of Wallach, which states that the racemic crystals tend to be denser from the respective ones of their enantiomers, thus it is expected to occur greater expansion of the cytoplasm of the cancer cell at the freezing point.

Since the time where Pasteur [1] discovered the existence of the enantiomers in nature with the separation of the tartaric acid in wine1 the study of the physicochemical properties of the racemic mixtures was followed. Regarding the crystallization of the racemic mixtures, this is done in conglomerates, racemic compounds, pseudoracemates, and quasiracemates. From those, conglomerates have always higher melting point from their enantiomeric analogues (Carnelley's law), especially with higher molecular symmetry, while the freezing point varies according to the racemic solution and its crystallization type. Thus, special research interest is focused primarily at the *in vitro* study of the crystallization type of the solutions of racemic mixtures from natural cancer proteins from various malignant neoplasms with their synthetic enantiomers, regarding the increase of their freezing point and their crystallization at higher temperature from that required for the crystallization of natural cancer protein solutions [2-8].

More specific, it is firstly suggested the *in vitro* laboratory study of the crystallization of cancer cell lines in relation to normal cell lines at the above described conditions, namely their culture in medium which contains solution of "anti-sense" enantiomeric proteins (with or without cryoprotective solutions) and with controllable lower of temperature and observation if crystallization, expansion and cancer cell rupture is occurring in contrast with the normal cell lines. It is also necessary to record with a special thermometer the exact temperature that the aforementioned goal is accomplished, in order to further investigate if it can be applied in living organisms and by which safe conditions.

Applications-indications

i) In patients with generalized metastatic disease (stage IV) in one or multiple organs, when the current anti-neoplastic treatment has no results. ii) In patients with local advanced disease without distance metastases, such as the generalized peritoneal carcinomatosis of the abdomen, as an alternative of multiple organs surgical resection or when a RO surgical resection is not feasible. The use of a type HIPEC technology machine, where, with the introduction of the therapeutic solution of the «anti-sense" proteins in the peritoneal cavity during the exploratory laparotomy, a lowering of the core body temperature will be caused instead, but with the concurrent use of the protective type "HILOTHERM" head cask for the maintenance higher temperature of the brain [9-13].

Arguments in favor of the particular research idea

The science of medicine uses successfully apparent extreme therapeutic methods, where for a smaller of greater amount of time the physiologic function of the organism is completed inhibited, in order the therapy of particular diseases to be achieved. Examples are: i) In Cardiology, the use of defibrillator or the intravenous administration of adenosine for the treatment of malignant arrhythmias by temporary pause of myocardial function and the new undertake (reset) of the sinus node, ii) In Anesthesiology, the administration of complete neuromuscular blockade and mechanical ventilation for the performance of major surgical operations, iii) In Intensive Care and Neonatology, the use of Extracorporeal Oxygenation Through Membrane (ECMO) for the support of critical pulmonary conditions (ARDS or the hyaline membrane disease of preterm newborns respectively), iii) In Cardiac Surgery, the administration of cardioplegia and extracorporeal circulation for the performance of transplantations, aortocoronary bypasses and other complex operations.

It is worth noticed that the controllable cooling of the patient causes the appearance of the mammalian diving reflex (submersion reflex) for the protection of the central nervous system. While at the current protocols of Cardiopulmonary Resuscitation, the therapeutic hypothermia is being used for in cases of circulation recovery after cardiac arrest and cardiopulmonary resuscitation for central nervous system protection [11]. In addition, in the international literature cases of complete recovery of hypothermic patients have been recorded after prolonged CPR without neurologic sequelae. Finally, the clinical experience shows that the majority of patients with malignant neoplastic disease are people with normal cardiovascular system, fact that increases the possibility of complete recovery.

Note of the writer Dr. Panagiotis Bouras, son of Christos and Christina Boura (genus of *Tzamou*): The above research idea has no intent to compete or replace the current pharmaceutical or other antineoplastic treatments and aims at the cases, where there is no current definitive treatment of the malignant neoplastic disease, as it is described in the applications-indications session. The above described

scientific methods may be reviewed, rechecked or replaced with newer, more effective ones, from fellow scientists, who wish to participate at the research study, carrying always my signature as verification, after my written information and consent and without any deviation from the basic research idea, as it is described at the introduction-aim-methods sessions. The successful future application of the particular method in humans with malignant neoplastic disease should always be governed by the principles of medical ethics and human moral values and care should be taken by the international, political, economic and social organizations and state institutions that all patients worldwide to have access to the specific treatment. The aforementioned therapeutic directions are currently theoretic, based on the international existing literature, and waiting for support for further evaluation, research and implementation from the medical community worldwide.

Conflict of Interest

There is no financial support or benefits if any from commercial sources for the work reported in the manuscript, or any other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

References

1. Pasteur L (1848) Memoire on the relation that can exist between the crystalline form and the chemical composition, and on the cause of the polarization Accounts Rendus Weekly of the Academy of Sciences 26: 535-538.
2. Cheighton TE (1993) Proteins: Structures and molecular properties San Francisco: WH Freeman p: 1.
3. Brown RJC, Brown RFC (2000) Melting point and Molecular Symmetry. J Chem Edu 77: 724.
4. Hylton RK, Tizzard GJ, Threlfall TL, Ellis AL, Coles SJ, et al. (2015) Are the crystal structures of enantiopure and racemic mandelic acids determined by kinetics or thermodynamics? J Am Chem So (JACS) 137: 11095-11104.
5. Karlsson JO, Szure EA, Higgins AZ, Lee SR, Eroglu A, et al. (2014) Optimization of cryoprotectant loading into murins and human oocytes. Cryobiol 68: 18-28.
6. Liu CC, Schultz PG (2010) Adding new chemistries to the genetic code. Ann Rev Biochem 79: 413-444.
7. Vutyavanich T, Piromlertamorn W, Nunta S (2010) Rapid freezing versus slow programmable freezing of human spermatozoa. Fertil Steril 93: 1921-1928.
8. Merrifield RB (1963) Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide. J Am Chem Soc 85: 2149-2154.
9. Scirica BM (2013) Therapeutic Hypothermia after Cardiac Arrest. Circulation 15: 2.
10. Joseph Wedekind (2004) X-Ray Crystallography: Fundamentals. Advanced Biochemistry BCH 408.
11. Glocker MO, Borhers C, Fiedler W, Suckau D, Przybylski M (1994) Molecular Characterization of Surface Topology in Protein Tertiary Structures by Amino-Acylation and Mass Spectrometric Peptide. Bioconjugate Chem 5: 583-590.
12. Panneton WM (2013) The Mammalian diving response. An enigmatic reflex to preserve life? Physiology 28: 28.
13. Hilmo J, Naesheim T, Gilbert M (2014) "Nobody is dead until warm and dead" Prolonged resuscitation is warranted in arrested hypothermic victims also in remote areas- A retrospective study from Northern Norway. Resuscitation 9: 1204-1211.

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