New integrative PDT method of cancer treatment by means of laser, magnetic therapy and herbal ferromagnetics

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ABSTRACT

Integrative photodynamic therapy (IPDT) of tumors consists of combined use of different curable factors that extremely increase the effectiveness of IPDT. The leading curable effect of PDT is determined by developing of aggressive photochemical reactions in the tumor. The main destructive factor of these reactions is the generation of free radicals that kill tumor's cells.

For PDT efficacy increasing it is necessary to solve the following problems and assure: easiness of production or synthesis; accumulation high selectivity regarding tumor tissue; low toxicity in light and darkness; singled oxygen generation high quant output; promptly elimination from the organism after the treatment procedure; good absorption in spectral intervals most transparent for tissues (red and infrared intervals); optimal interconversion between quant output and fluorescence quant output.

PDT effectiveness may be significantly increased by means of: increasing of photosentisizer selectivity and accumulation in tumor tissue; increasing of tumor tissue photochemical destruction caused by photosensitizer.

Realization of integrative PDT using Cyber Laser may increase tumor therapy effectiveness to 94–96% and at the same time will establish a new direction in PDT.

KEY WORDS: integrative photodynamic therapy, cancer, tumor's cell

Integrative photodynamic therapy (IPDT) of tumors consists of combined use of different curable factors that extremely increase the effectiveness of IPDT. It is known, that the leading curable effect of PDT is determined by developing of aggressive photochemical reactions in the tumor. The main destructive factor of these reactions is the generation of free radicals that kill tumor's cells [1]. Classic PDT includes only four stages, versus eight stages of IPDT offered by me (every added stage considerably increases treatment's efficacy). The first stage of the classic DPT is intravenous or by other route administration of photosensitizer. In the second stage (the duration of the stage is dependent upon the sensitizer's metabolism and the speed of its accumulation in the tumor) assessment of proportion of sensitizer's concentration in healthy tissues versus the tumor is performed; besides, by means of photosensitizer's fluorescence tumor location and size are revealed. The third stage is tumor exposing to laser certain wavelength for 10–25 minutes. In the fourth stage (duration is 10–35 days) toxic photochemical reactions destroy the tumor and restitution of affected tissues occurs [1, 2]. Thus, for PDT efficacy increasing, the following problems should be solved.

The first group of problems includes items that are associated with PDT sensitizers. Optimal sensitizer should meet the following requirements:

- be easily produced or synthesized
- have accumulation high selectivity regarding tumor tissue
- have low toxicity in light and darkness
- have singled oxygen generation high quant output
- be promptly eliminated from the organism after the treatment procedure
- be well absorbed in spectral intervals most transparent for tissues (red and infrared intervals)
- provide optimal interconversion between quant output and fluorescence quant output.

Correct photosensitizer selection is important, but not the only prerequisite for PDT effectiveness. The main limiting factor of PDT is the depth of its action. At present, photodynamic action spectrum of clinically used medications is from 620 nm to 675 nm [3], at the same time the transparency of biological tissues regarding this spectrum is low – only a few millimeters. The maximum transparency of the tissues is in the far-red and short infrared intervals (750–1500 nm) and this corresponds to the generation interval of many lasers. So, revealing or elaborating photosensitizers capable of providing singled oxygen effective generation in this spectrum interval may dramatically increase PDT effectiveness. It is known that in many different types of tumors there are common metabolic features and pathogenic chains that discriminate them from healthy tissues. Pyruvate kinase, hexokinase and phosphofructokinase enzymes' extremely high activity is a characteristic metabolic feature of tumor cells [4]. As a result, anaerobic glycolysis occurs. An increase of activity of enzymes that take part in the synthesis of the precursors of nucleic acids, purine and pyrimidine nucleotides in tumor cells also occurs. Lactic dehydrogenase V isoenzyme activity considerable increasing and lactic dehydrogenase I activity decreasing is very specific for tumor cells as well. Dramatic disproportion between glucose influx and its metabolism speed in tumor cells decreases glucose amount in the cell to the zero. Besides, tumor tissue has lots of other specific features that have role and importance in PDT and we will discuss them later [1, 4].

As it was mentioned, all tumor tissues have common features that differ them from healthy tissues, but at the same time, there are metabolic differences between tumor tissues determined by their localization, genesis, morphology, etc. So, the following important conclusions may be drawn:

1. Photosensitizers used for PDT can not be universal for all kinds of tumors because tumor tissues with different morphology and different photosensitizers can not be in the same absorption spectral interval.
2. For any certain tumor group appropriate optimal photosensitizers' data bank or base should be elaborated.

PDT effectiveness may be significantly increased by means of [5–8]:

- increasing of photosensitizer selectivity and accumulation in tumor tissue
- increasing of tumor tissue photochemical destruction caused by photosensitizer.

Photosensitizer accumulation selectivity toward tumor tissue is provided not only by metabolic differences in healthy and tumor tissues, but by intercellular space characteristics as well.

Issuing from the above we have elaborated a principally new PDT method that includes the following:

A. As it has been mentioned, tumor tissue is able to absorb a great quantity of glucose for a very short time and to metabolize it 14–17 times faster than healthy tissues. In tumor cells anaerobic glycolysis dominates, so using their "greed" regarding glucose it is possible to increase PDT effectiveness by loading the organism with n-concentration m-quantity glucose and other carbohydrates during the B stage of PDT. The speed of glycolysis in tumor cells considerably surpasses citric acid cycle capability there, so pyruvate production greatly exceeds its need and as a result lactate accumulation

and local acidity increasing occur. So, decompensated acidosis takes place in tumor tissue. Acidosis causes destruction of the tumor tissue by means of local blood circulation arrest, photosensitizer's photopathogenic potentiation and medium pH decreasing. Medium pH decreasing also facilitates tumor tissue photochemical injury. Besides, the use of glucose and other carbohydrates in PDT may have a diagnostic application as well.

B. Photosensitizer photochemical destructive effect enhancement is extremely important not only for increasing of treatment effect, but also for considerably decreasing of photosensitizer dose administration. The latter is necessary because during the photosensitization reaction lots of products are generated and they are able to accumulate in the organism. It is especially typical for parenchymal organs with high metabolic rate. Besides, in many cases the patients have individual hypersensitivity and different kinds of allergic reactions to administered photosensitizers. For mitigating these undesirable side effects and enhancing of PDT therapeutic effects we are offering the following:

1. Local injection of certain medication by means of special poly injector (the construction and functioning principle of the device will be explained in "Cyber Laser" chapter). This approach may increase the speed of tumor tissue destruction caused by PDT. Particularly, such properties are typical for positively charged local anesthetics. For local poly injections we have offered n-concentrated ethanol, that entirely corresponds to potentiation of the mentioned effect.
2. PDT effects may be substantially increased by causing of local hyperthermia. It is known that temperatures higher than 39 degrees centigrade suppress tumor cell vitality. 42 centigrade temperature for an hour irreversibly destroys tumor cell, temperature interval 42–45 degrees centigrade destroys tumor cells much faster. PDT effectiveness considerably grows in combination with magnetic field action. In this combination magnetic field action occurs by means of several different mechanisms.
3. CL has a micro poly injector that allows to perform injections directly into tumor. The injector is able to follow precisely tumor contour and to inject into tumor carbohydrates, ethanol, photosensitizers, etc. From this point of view direct injection into tumor Fe-containing substances is extremely promising because tumor cells have very high affinity toward Fe-containing agents (Fe salts, ferritine, transferrin, etc.). For PDT some plant substances and herbs that contain Fe and ferritine may be used. They besides direct photosensitizing effect can provide certain concentration of ferromagnetics in tumor tissue. Interestingly enough, Fe salts are good photosensitizers. Fe presence in tumor cell may be very effectively used for increasing cell temperature till 46 degrees centigrade by means of magnetic field. Such temperature causes tumor tissue lysis. Combination of magnetic therapy combination with PDT dramatically increases the effectiveness of the treatment. Without explaining molecular mechanisms briefly the following should be stressed:
   1. Magnetic field of certain intensity may induce free radical generation, particularly, oxygen active forms production. The latter are the main killing factor in PDT (superoxide anion, radical-singled oxygen).
   2. The majority of enzymes that participate in anaerobic glycolysis are magnetic field sensitive.
   3. Magnetic field strongly modulated photobiological and photochemical reactions and it may be accompanied by chemoluminescence.
   4. Magnetic field of certain power can induce photochemical reaction it self, without a photosensitizer.
   5. Magnetic field therapy combined with administration of Fe salts and ferromagnetic containing photosensitizers can cause tumor destruction both by means of hyperthermal and photochemical mechanisms.
   6. Magnetic field used in PDT may establish a new direction in PDT, in particular, PDT performance without photosensitizers in form of combined laser and magnetic field therapy plus mentioned integrative methods. PDT without photosensitizer implies endogenic porphyrins concentration increasing in organism by means of either their synthesis stimulation or administration of their natural precursor – α-aminolevulinic acid (ALA-PDT). In this case protoporphyrine IX and its complex with Fe – protohem – via feedback mechanism regulate the activity of the precursor synthase that causes accumulation of a great amount of endogenic porphyrines in the organism. Integrative PDT method includes also computer cybernetic component that contains data (information bank) regarding photosensitizers and ferromagnetics, visual differentiation block, DD matrix and interface (Cyber Laser).

Cyber Laser functions on the base of Nd:YAG laser, but for treatment of psoriasis, vitiligo and some other problematic diseases it should also have ultraviolet spectrum; for color light therapy light filters and all colors of visible spectrum are needed.

Thus, realization of integrative PDT using Cyber Laser may increase tumor therapy effectiveness to 94–96% and at the same time will establish a new direction in PDT.

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