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Review Article

The Efficacy and Safety of Head and Neck Cancer Treatment using Photodynamic and Ultrasound Therapy: A Systematic Review

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Abstract

Despite the improvement in therapeutic and diagnostic techniques in the medical care of head and neck tumor, the results and survival of patients has remained poor. This mainly is as a result of late detection and the ability of the disease to develop loco-regional metastasis. The primary way to control it is early detection and treatment to prevent recurrence and metastasis. Conventional treatment of these neoplasms involves the use of photodynamic treatment and ultrasound therapy. These treatments have proven to be efficacious, however, they have at times ended up causing damage to healthy as well as dead tissues, worsening the previous issues as a result of the complicated anatomical structure and procedure applied in their treatment. The use of photodynamic and ultrasound in the treatment of head and neck cancer (HNC) was established more than two decades ago. In this review, we will focus on the on assessing the efficacy and safety of HNC treatment using ultrasound and photodynamic therapy.

Introduction

Photodynamic therapy (PDT) is a mechanism that rely on the reaction of photons and chemical activities between a photon induced molecule (photosensitizer) that is typically placed between the electromagnetic spectrum and molecular oxygen. These compounds usually cause no harm when placed independently but upon amalgamation, they lead in the formation of reactivated oxygen species (ROS). These ROS have the ability to activate cellular destruction to cell membrane and organelles depending on where they are produced [1]. PDT procedure is composed of two stages. The first is the administration of PS and the second is the light exposure. These stages portal highly minimize hazardous effects as the inoffensive PS is induced only through direct radiation which leads to local tissue damage. Various research has proven the effectiveness of PDT in medical care of early stages of HNC. The studies have demonstrated that the procedure provide acceptable outcomes when used in the medical care of T1 or T2 SCCs of the glottic larynx and oral cavity [2]. The key advantages of PDT are that it can be safely re-administered, the PS has few negligible side effects, it heals with negligible scarring, and that it does not preclude further surgery or radiation. The primary disadvantages are photosensitivity of a period of up to six weeks, cost of FDA approved drugs, and pain.
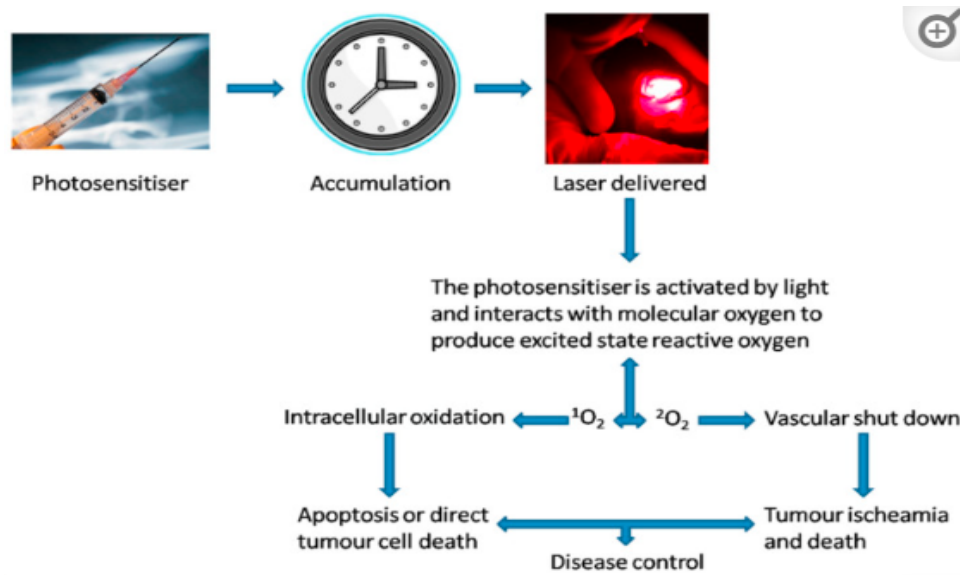
Mechanism behind the stages of PDT administration.

Ultrasound can also be used as an analytic imaging mode and as a therapeutic mode where photons are localized in the body to activate different biological properties. Low intensity ultrasound has a wide therapeutic application in medicine. Combined with activating molecules it has also been applied in cancer cells through sonodynamic treatment; to influence cells and their elements directly; for its anti-vascular reaction on cancer neovasculature and for RNA delivery to enhance bone and tissue healing and heating [3].

The insonation of neoplasms is easy to perform with low-intensity ultrasound because it does not require a beam that is precisely localized, the bio-effects of adjacent tissues is minimal, the procedure is relatively cheap since the apparatus used are not expensive and it is easy to work on activation microbes and molecules localized in lumes of the tumor neovasculature. Despite the fact that the period of treatment is long when compared to the application of highly intensive ultrasound, dose fractionation or repeated treatment is easily performed without causing any harm. The potent of ultrasound for medical care effectiveness also involves the danger of unexpected severe biological effects that can lead to serious patient injury. Therefore, measures such as standardization, side-effect risk minimization, and ultrasound dosimetry should be carefully considered to maximize and insure patient outcomes.

Background

The administration of second-generation PS result for early-stage handling HNC leads in better cosmetic and clinical results in the absence of severe effects of the long-lived skin photo-reaction experienced prior the administration of first-generation PSs. With the use of second-generation PSs in PDT, savior dysplasias, oral and CIS cancer cells have shown better expectations of CR results and low AE. Studies have indicated that HPPH-PDT can safely be applied in the medical care of first stage HNC and have a 85% CR at the highest abided dose (198). With patients that required recurrent respiratory papillomatosis within every three months, mTHPC-PDT led in recorded effectiveness of laryngeal illness over time with a reoccurrence of three mild oral and precancerous cuts have diagnostic capacity similar to those observed in main surgical procedure. The application of mTHPC on mild dysplasia to chronic dysplasia to CIS or 5-ALA on thin to average dysplasia lesions, PDT successfully resulted in CR or condition steadiness for a sufficient period of time. For mild risk lesions, CR ranging for a long term is achievable through mTHPC-PDT with a range of three to five years rate of survival of 92% and 84% respectively in comparison to standard treatment [4]. Studies examining mTHPC-PDT medical care of oropharynx squamous cell cancer indicated effective treatment rate of the rates of 86% for cancer of the oral SCC and lip later a check-up of 37 calendar month. The studies reported good cosmetic and functional results.

Persistent and recurrent nasopharyngeal carcinoma (NPC) and chronic HNC are critical issues in HNCs as conservative medical care choices are mostly fatigued. After the discovery of varying lighting techniques, example the nasopharynx applier and interstitial lightings, these cuts can be treated using PDT medical care. Handling of nasopharyngeal cancer with mTHPC-PDT leads to CR and lengthened patient survival [5]. Studies developed through ultrasound directed internal PDT for inner-channeled tumors exhibited promising outcomes where almost all patients indicating enhanced QoL and enhancement of limb performance.

mTHPC-PDT have also proven to be a harmless ancillary treatment for repeated cancer growths of the paranasal venous sinus and repeated sinonasal head malignant cancers [6].

mTHPC-PDT indicated effectiveness that can be achieved with surgery at initial period HNC and minor cuts. For bigger cuts, surgical procedure is further effective after all the therapies has been completed, however, it is result to higher illness. As a relaxing therapy, PDT is more effective compared to standard care.

Principles of photodynamic treatment in the therapy of HNC

Photodynamic reaction

Despite the fact that the mechanisms of photodynamic therapy (PDT) are still under investigation, it has been proven that its molecular paraphernalia are grounded on the response of photon catalyzed photosensitizer (PS) with other molecules that creates radicals [7]. The radiation of a PS result to the engagement of photons and a shift of the photosensitizer to its exited level of a higher level. Since this condition is unbalanced, the PS can assume its inactivated level by changing its stage of energy into fluorescence or heat, an energy state that can be used for optical monitoring and diagnostic [8]. In other cases, intersystem crossing can be experienced leading to the status of the PS to be activated to trio state T1. In this triplet condition, the PS can exchange its energy level by bumping with other nucleus or by phosphorescence leading to the creation of chemically reactive compounds through reactions of two types [9]. The single state T1 can interact with different carbon-based solvent or substrates and transference protons or electrons to form essential cations and anions respectively. A type I reaction is formed when photosensitizers counter with electron providing substrates to produce PS that later interact with oxygen to produce superoxide radicals. Type II reaction takes place when T1 react with non-reactive oxygen $^3O_2$ through the localization of photons to create singlet oxygen $^1O_2$ which is a very reactive oxygen species (ROS).
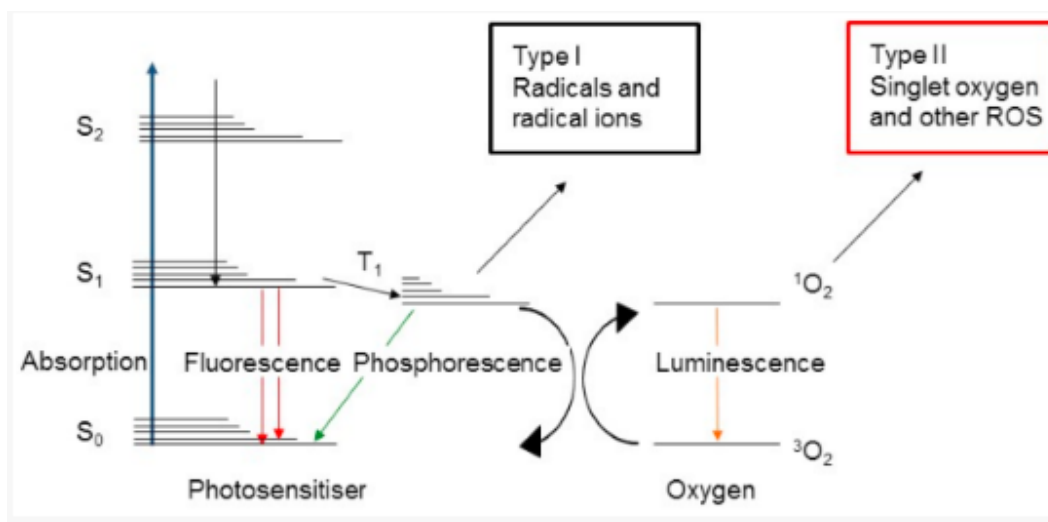
Diagram for type I and type II reaction after PS induction after light induction

The formation of superoxide and anions of oxygen will lead to cytotoxicity since the two elements can readily react with biomolecules such as nucleic acids, protein, and lipids leading to their damage [10]. Type I reaction leads to the formation of superoxide that are not directly harmful in biological system; however, they have a tendency of forming section of a response that leads to the production of hydrogen peroxide. Reaction of superoxide anions with hydrogen oxide through Fenton reaction result to the formation of reactive hydroxyl radicals that can easily add to abstract hydrogen atoms or double bonds of almost all biomolecules [11]. This type of reaction can result to membrane damage.

Most photosensitizers tend to react via type II cycle where singlet oxygen is the main molecule leading to the impairment of oxidative cellular. The chemical reaction of membrane lipids and singlet oxygen result to lipid peroxidation leading to impairment of cellular skins. Singlet oxygen reaction with amino acids might also lead to disruption of vital protein functionality. The short lifetime radius of singlet oxygen and the localized photosensitizer activation through illumination of target tissues makes photodynamic therapy controllable and very specific. This also indicate that the distribution of the PS effect the target of PDT and the subcellular stage [12].

Photodynamic therapy at cellular level

Photosensitizer localization is the main factor that regulates cellular response to photo damage. The target site of intracellular reaction depends on PS and takes a vital function in predicting the outcomes of the cell. Study associating the significance of PS subcellular site with intercellular effectiveness in activating cell extermination indicated that the PS crystal violet (CV) that had reduced ability in the production of radicals is equally effective in activating cell termination as methylene blue (MB) that has the ability to produce ten times as much radical. This is as a result of the cytolocation of the MB and PSs randomly distributed to the lysosomes and cytosol whereas CV is deposited in mitochondria, indicating that distribution is highly significant compared to the number of radical produced. The characteristics of a photosensitizer will determine its localization towards organelles like the lysosomes, plasma membrane and mitochondria [13]. The cell adhesion properties and cytoskeleton also form part of PS target. Despite the fact that photodynamic reaction influences various site of action, three key pathways (apoptosis, autophagy, and necrosis) of photo damage activated apoptosis will be covered in this review. The capability of PDT to induce cell death channels avoid the issue of programmed cell death resilient cell in tumors, that are primary problem for other carcinoma treatment [14].

Programmed cell death

Apoptosis

Apoptosis is a modulated process of programmed cell-death with efficiently controlled mechanism [15]. This pathway can be induced through various mechanism after PDT-activated impairment of numerous organelles. Photosensitizers that confine to mitochondria are the once with a higher potential of inducing programmed cell death [16]. This can be attributed to the fact that mitochondria takes a significant duty in most of programmed cell death mechanisms and it is expected that changes to these organs will lead to programmed cell death [17]. Mitochondrial photo-alternation activates easy penetration of its membranes resulting in the deposition of cytochrome c into the cytosol [18]. This consequently led to the activation of the caspase modulated apoptotic mechanism.

Necrosis

With severe cell damage, factors of the apoptotic mechanism can be damaged leading to poor execution of apoptosis. Higher level of apoptosis is experienced resulting to necrosis instead of programmed cell death in cases of higher PDT-dose administration depending on the level of light and PS [19]. Necrosis is also frequently observed in cases where the PS target of is the membrane. When compared with apoptosis mechanisms, necrosis is viewed as being less regulated. Plasma membrane as a result of photo damage lead to the release of intracellular material to the surrounding cells resulting to inflammation [20].

Autophagy

Cells have the ability of recycling damage cytoplasmic and organelles elements by autophagy mechanism. The altered cells are covered by a dual layer membrane known as auto phagosome which reacts with lysosomes to damage its properties [21]. Despite the fact that it is well-thought-out as a cytoprotective process, autophagy has also been proven to be a means that led to cell death in response to photodynamic therapy [22]. When apoptosis is damaged, autophagy remains the primary mechanism responsible for cell death [23]. This process is dependent on the level of dose of PDT. Low administration of autophagy acts as a protective method while high level of administration of the dose can result to the activation of cell death [24]. The distribution of PS is also vital as ER- and mitochondria-targeted PS activate a pro-survival autophagy response while lysosomal-focused PS can hinder cells self-degradation [25].

Generally, it's complicated to ascertain the results of PDT in the cells. However, it can be observed that high PS localization level and high dose of PDT in the plasma layer, mortification is the most leading cause of apoptosis of cell death. In cases of low level of PDT or PS distribution to the plasma skin, the leading cause of apoptosis is mortification. Apoptosis is activated in cases of low-level PDT activated alteration to the anti-apoptotic or mitochondrial mechanisms. The induction of mild PDT alteration to organelles lead to the activation of autophagy to enforce and prevent the alteration. Nevertheless, in cases where the ability of programmed cell death is overcome or conceded as a result of lysosomal alteration, a programmed cell death can lead to apoptosis. Explaining the actual outcomes of PSs and consequent outcomes in the cells is vital for the understanding of the effects of photo dynamic therapy.

Photodynamic treatment effects at a tumor level

The negative photons result of photodynamic therapy treatment are not malignant growth discriminating. Localized photosensitizers react with both tumor and healthy organelles. Normal tissues have the ability of clearing or eliminating the PS in the long run while tumor cells cannot as a result of lack of lymphatics. This result to the leakage of PS cancer tumor cells, which when amalgamated with localized induction by desired photon result to PDT selectivity. Different theories have been developed to explain the factors that stimulus the choosy growth of PS in cancer neoplastic cells. One of the main theories that covers all the PSs is grounded on morphological variations between tumor and healthy tissues. The fast and uncontrolled growth of tumor cell leads to the formation of abnormal vasculature solid tumors that have unregulated inner lining. Consequently, due to the leaky nature of tumor endothelium, macromolecules can erupt outside

the blood vessel region. They are also reserved for a lengthier time linked to healthy cells as a result of the defective lymphatic leakage in tumor cells a process of cancer treatment referred to as Enhanced Permeability and Retention (ERP) [26].

PDT have three principal pathways of malignant tissue alternation in HNC. The first mechanism is where the distribution and induction of the PS cancer tissue leads to the generation of ROS which can directly kill carcinogenic tumors. The second mechanism is where PDT targets head and neck tumors vasculature restricting oxygen supply and other important minerals. The 3rd is the PDT induced resistant system that activate resistant and inflammatory action against cancer cells.

The effects of direct reactive oxygen species

Just as the subcellular, photodynamic therapy target is significant for the final outcomes of malignant tissues in head and neck cancer. Tumors are composed of the parenchyma made up of the cancer tissues and the stroma, that acts as the vascularized supportive cells. Growth stroma make up more than 90% of tumor mass [27]. Stroma is required in all solid tumors for growth since it provides the essential minerals and oxygen and controls unwanted material clearance in the blood vessels [28]. There are different end results of PDT depending on the part affected by head and neck cancer. The prevalent growth alternation caused by photodynamic treatment is the damage of parenchyma tissues. Photosensitizers that localized in in growth parenchyma leads to cell damage followed by tumor cell necrosis or apoptosis. Since instantaneous damage of neoplastic tissues is not sufficient for cancer treatment, damage of growth stroma takes a key part in PDT effectiveness. PDT activated structural protein damage like the integrin's can upset important stromal-growth signaling [29]. Consequently, tumor progression is restricted by the destruction of stromal fibroblast and can result to an increase in healthcare results by relaxation the malignant tissue extracellular matrix [30].

The spontaneous cell death response of photodynamic therapy on both stroma and parenchyma can be altered by the type of generation of reactive oxygen species when there is the sufficient supply of oxygen. Lack of properly grown vasculature leads to improper vasculature growth of tumor tissues resulting to insufficient delivery of both PS and oxygen. In HNC, tumors that are similar have varying PS distribution depending on their vascularity. Damaged vascularity acts as a hindrance in instantaneous PDT modulated malignant tissue damage.

Vasculature effects on PDT

In tumor development, development of new blood vessels or angiogenesis is a major process [31]. The significant of tumor vasculature can be proven with by the presence of low oxygen region and necrotic in tumors that result from the unorganized development of blood vessels. Restricting the formation of new

vessels or damaging present vasculature have negative effects for tumor proliferation. This makes anti-angiogenic to be a clinically approved healthcare procedure for the medical care of cancer [32]. Damaging of tumor vasculature in HNC is has been marked as a significant factor in PDT efficacy. An example is how most of hematoporphyrin derivative (HPD) is significantly influenced by the disruption of blood flow [33].

After the administration of photodynamic therapy, subendothelial and endothelial cells are damaged. When the period between photosensitizers localization and illumination is reduced, the direct damage to vasculature is increased significantly [34]. This indicates the effects of vascular alternation on PDT activated malignant tissue damage.

Intravascular photodynamic therapy destroys endothelial cells making them to multiply, broadening the interendothelial tissue intersections and revealing the adjacent cells. The destroyed endothelial cell might emit clotting elements like the von Willebrand element, inducing platelets [35]. The induced platelets react with the subendothelium that have been exposed resulting to platelets activated vasoconstriction after the administration of PDT, leading to further restriction the flow of blood [36]. In time, the interacted blood blow and damaged blood vessels will read to tissue hypoxia, tumor death, and nutrient deprivation. To increase PDT therapeutic efficacy, some medical practitioners tend to implement the idea of vascular channeled PDT. Research associating cellular aimed photodynamic therapy with a vasculature directed mechanisms by modulating the DLI indicated that effectiveness amplified when malignant tissues vasculature was acted upon with a short DLI [37]. Amplified effectiveness was also recorded when PDT and vasculature modulated mechanisms were done in repetition to act on both the vasculature and malignant tissues parenchyma [38].

Enhanced therapeutic treatment can be attributed to long term tissue hypoxia. When determining the tissue oxygen capacity in the process and after vasculature targeted photodynamic treatment, PO_2 decreased highly in the process of both approaches as a result to the creation of reactive oxygen species. Nevertheless, in photodynamic treatment, cell oxygen capacity have a fast recovery but after blood vessel system modulated PDT this kind of healing is not observed. After PDT cell reoxygenation decreases its treatment results. However, this can be evaded by destroying vasculature ascertaining prevalent hypoxia and enhanced treatment results. The blood vessel damaging outcomes of PDT are a key factor of PDT efficiency.

Immune reaction

The induction of an instigative reaction that is accompanied by internal cancer resistance is the third mechanism of photodynamic activated tumor annihilation. PDT-activated oxidative pressure can stimulate the development of heat shock proteins (HSPs),

flow factors associated to instigative and production of incendiary cytokines [39]. Cancer cell destruction is followed by the production of nutrients such as proteins and other cells known as damage-associated molecular patterns (DAMPs) that can cause a solid instigative response. When PDT has been administered, HSPs such as HSP70 are activated and can what's more be expressed on the cells exterior or are in instance of mortification they can be produced outside the blood vessels [40]. HSP can combine cancer malignant tissues and react with Toll like receptors (TLRs), which is a primary rout of inducing antigens producing cells (APC) [41]. Consequently, these reactions controlled the expression of activation and resistance reactions of RNA. The source of HSPs and other DAMPs can change with accordance to the subcellular site of PDT reaction [42]. Other DAMPs experienced following PDT are skin damage end results such as metabolites of arachidonic acid and lipid fragments, ER protein calreticulin or ATP [43]. Internal resistance cells such as dendritic cells (DCs), lymphocytes, and macrophages are controlled by DAMPs in the process of inflammation to improve tissue healing and remove cellular debris [44]. The increased activation and expression of transcription components such as induction protein 1 (AP1) is a major pathway in activating an activation reaction after PDT activated oxygen addition reaction. Different research with varying PSs indicated stimulation of transcription components following PDT. These transcription elements initiate response of instigative cytokines such as cancer mortification factor (TNF)- α interleukin (IL)-6 that activate neutrophile. Consequently, an upregulation in the response of cell adhesion cells is an act that enhance neutrophilia relocation [45]. The sum of revolving neutrophiles when PDT is taking place plays a key part in defining PDT efficiency. Neutrophiles does not only eliminate photodamages tumors but also unswervingly influence tumor-channeled T cell endurance and control the production of tumor resistance after PDT [46]. After the instant activation reaction of the native resistance mechanism, internal cancer immune resistance can advance. Anti-cancer resistance was discovered when lymph node molecules from photodynamic therapy was administered in experimental subject were administered to unprecedent experimental subjects and activated destruction of ensuing tumor encounters. Experimental sample subjects that were administered with PDT indicated resistance upon encounter with developed cancer encounters following not having any malignant tissues for a period of about three to four months after PDT, proving that there was an establishment of an immune memory [47]. The significance of the lymphoid tissues in life time PDT efficiency was ascertained after the entire tumor cells responded to PDT and degenerated in both bone marrow or immunocompetent T-cells to resistance deficient experimental subject led to the production of reactivation of lengthy malignant tissues response to PDT and damaged growth reproduction [48]. Despite the fact that the adaptive response is not significantly vital in the preceding growth impairment, it influences the internal cells significantly for reappearance of comparable growths by creation of growth-associated remembrance tissues [49]. The severe instigative reaction after PDT lead to the phagocytosis of necrotic and apoptotic malignant tissues creating the principals of this pathways. The DCs that are not fully developed, that form part of the preceding phagocyte army, eliminate dead cells and cellular debris, hence being able to produce and present antigens [50]. The malignant tissues producing DCs react with CD4 helper T-lymphocytes that can later induce CD8 cytotoxic T-lymphocytes (CTL), despite the fact that T-helper tissues self-governing induction of CD8 T-tissues has been defined [51]. The CTLs have the ability to identify malignant tissues and activate apoptosis. The capability to activate anti-cancer resistance following PDT has initiated to the development of a need to come up with PDT produced cancer vaccines that can be used as either a therapy or prophylactic.

The effects of photosensitizers in photodynamic therapy

Photosensitizers are separated in different groups grounded on the period of their discovery and their individual features. The third group of PSs are the once being applied in clinical treatment today. They are altered second group PSs with biological conjugate solution such as antibodies, transporters, or liposomes to enhance their therapeutic, physical and chemical components. These characteristics make the tumor to have active cite of action resulting to high sensitivity. This henceforth leads to administration of reduced quantity and less undesirable damages. PS are similarly premeditated in a way that they can absorb of the most preferred wavelength for enhanced tissue penetration [52].

Factors affecting photodynamic therapy efficacy

Light

The treatment efficiency of PDT relies on the components of the electromagnetic wave spectrum utilized in the induction the PS. In an outward method, it has to go through skin membrane and tissues to influence the cite of action and induce the PS internally. In an intraluminal design the positioning of various bases of light is a vital point of consideration. Light penetration in the tissues is a multifaceted approach which relied on the photosensitive components of the tissues at the electromagnetic wave spectrum of used light. There is noteworthy uniformity within and between matters and the multiple molecules affecting photon scattering and absorption. At shorter visible spectrum, effectiveness can be reduced because of captivation by endogenic chromophores like hemoglobin, on the other hand at lower spectrum water can captivate photons. This regulates the series of spectrum to optically diverge through tissues at a range of between 600-1300 nm. In cases of wavelength longer than 850 nm the illuminated photons do not deliver significant wavelength necessary to induce the photosensitizer to its triplet condition and to yield singlet oxygen.

It is therefore clear that the therapeutic period for most of PDT analysis falls in the red location of the wavelength ranging from 620-850 nm reaching an ideal tissue infiltration PS induction [53].

Both incandescent and laser light have been proven to be efficient for the delivery of light [54]. It is unlikely that a one source of illumination can be used in various type of PDT and the source applied should be the right one for the PS absorption spectrum, usability, and type of diseases. Lasers are applied in clinical PDT and can be merged with optical fibers that can used internally to illuminate tumors that are located deeper by use of diffusion tips. The method used in the application of light in PDT is also of great significance when ascertaining the therapeutic efficacy of the procedure. Dissimilar illumination procedures with the identical source of light might have varying results in PDT. High energy density levels might reduce the amount of oxygen in malignant tissues very rapidly, inhibiting the effectiveness of PDT [55]. Light fractionation and light measure regimens impact the primary anti-cancer response [56]. Light quantity schedules mostly depend on the type of case at hand. It is therefore important to understand light dosimetry in the application of PDT.

Oxygen

The accessibility of adequate oxygen in the tissue is important in ensuring the effectiveness of cancer diagnosis. The existence of oxygen starving sites in malignant tissues is a main hinderance in compact tumor therapy. One of the major reasons behind hypoxia hinderance is that oxygen starvation is usually activated by damaged cancer vasculature, therefore indicating that the channels of medication distribution are destroyed. Additional goal in the significance of oxygen of is treatment effects of phototherapy. In photodynamic treatment, the production of higher energy state oxygen requires oxygen that have not been activated indicating that the oxygenation of tissues highly determines PDT efficiency [57]. The existence of active hypoxic sites in tumors increase resistance to PDT efficacy since areas with low levels supply of oxygen are well-thought-out to be PDT resilient [58]. This can be ascertained by the ablation of the effects of PDT in cases where the key vasculature of a malignant tissue is blocked. Improving the supply of oxygen in tumors by pyperbaric oxygen treatment enhances cancer reaction to chemo- and photo-therapy. However, in PDT altering the pressure that will be exerted by oxygen in vasculature has limited to no outcome on the level of oxygen supplied to the cells that are far away from the small blood vessels where oxygen is required for photodynamic treatment. The development of reactive oxygen species leads to oxygen exhaustion in the process of PDT liable to the illumination intensity. Indeed, the vascular damage after PDT enhances the reduction of the level of oxygen being supplied to the tumor. By regulating illumination and PS level of dosage, cases cause by such phenomena can be avoided.

Photosensitizer uptake and distribution

Because of the reduced target are of ROS and specifically higher energy state oxygen, accurate distribution of PD is considered vital for its treatment results. Having adequate knowledge and modulating PS distribution significantly enhances the performance of PDT. From the time when treatment start until the moment the PS have reached the site of reaction, different chemical, biological, and physical processes take place influencing the final setting of the photosensitizer. An instance is where PS have been taken intravenously, the PS initial react with fluid protein forming a bond. Diverse PS react in a different way with serum proteins hereby influencing the response of the dosage and their localizations respectively. The PS is required to go through the vasculature to get to the targeted growth, therefore, reacting with these cells or matrix outside the cells and those within the malignant tissues. Research have also proven that total charge, energy localization, lipophilicity and the whole mechanism entirely influence subcellular distribution and cellular uptake of a PS and eventually influence the medical care outcomes [59].

Charge

The available energy of a photosensitizer influences the association between cellular membranes and PS. Since plasma lemma has an electronegative, PSs that are negatively charged assume reduced transmembrane localization in comparison to electropositive PSs, which easily move from one membrane to another [60]. Positively charged PSs have free movement across the cellular membrane and when in the cells, they mainly move in the direction of the mitochondria membranes [61]. Comparison of epoxide of varying energy and energy localization are equated for their uptake and distribution, mano-positively charged epoxide moved in the direction of the membranous sections of the cellular membrane, ER and Golgi, whereas the more positively ionized elements preferentially shit to the mitochondria [62]. Inactive localization accompanied by mitochondrial transportation is replaced with a process where anionic PSs are absorbed through phagocytosis which initiates lysosomes distribution. Low electronegativity of ions can be replaced by lipotropic oleophilic [63]. The significance of electrons localization is evident in cases where same ionized electrons but varying localizations are likened. The placement of a charge in a varying molecule can alter with its accessibility and destroy the association charges between PS and membrane. Altering PS entire charge and charge distribution plays a key role in shaping its subcellular distribution consequently photodamaging effectiveness.

Lipotropic Oleophilic

Changing the lipotropic oleophilic of a PS affect its cellular localization therefore affecting its distribution and uptake. The most water loving PS generally associate with albumin while the

amphiprotic photosensitize form attract lipoproteins with high-density and the once that are water hating that are treated with solubilization carrier, generally move to the upper internal lipid center of lipoproteins with low-density. The high predilection for membrane reactions of more lipotropic oleophilic elements enhances their movement in the direction of mitochondria [64].

3D shape

The absorption of photosensitizer also relies on the 3D form of the cell as varying analogue with the same electron charge and lipotropic oleophilic indicates varying behaviors. This can mostly be attributed to spatial availability of charges. It can therefore be concluded that, apart from lipophilicity and charge, the model of a molecule can take a vital part in malignant tissue penetration and photodynamic treatment effectiveness.

An ideal photosensitizer

For a PS to be considered ideal, it should several preferential characteristics. One of the expected properties is that it is required assume minimum dark harmfulness and preferably it should be non-toxic. PS should also be easy and feasible at point of administration using different channels and should not inflict any discomfort. It

is also expected to have higher band of absorption for maximum tissue uptake, and have sufficient energy to produce higher energy state oxygen. It is also required to have high production of ROS in the process of illumination. Lastly, it should be pure and have an easy production process and should be stable enough to facilitate long storage.

Principles of ultrasound in the treatment of HNC

Sonodynamic treatment

The term sonodynamic treatment is derived from photodynamic treatment. Sonodynamic is facilitated through ultrasound-activated cavitation and sonosensitizers to form unrestricted radical that destroy neighboring fast dividing tumors unlike in photodynamic therapy where PS are activated spontaneously upon illumination to form ROS [65]. The main advantage of sonodynamic therapy is its diagnostic continuous, low-intensity ultrasound frequencies that have the ability to treat deeply located tumor cells. Compared to ultrasound therapy, PDT applies visible light spectrum which weakens quickly in molecules has restricted uptake and can be used selectively intra-operatively or superficially. Ultrasound has a moderately high rate of tumor growth restriction.
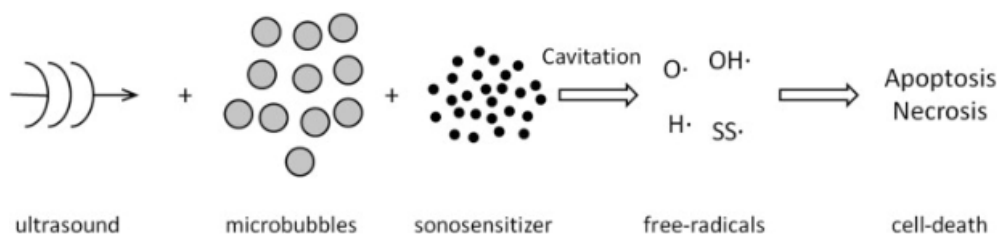
Schematic representation of sonodynamic treatment mechanism where mild insonation tumor molecules in the existence of a sonosensitizer cause to cavitation, resulting to the release of unrestricted positively and negatively ions which result to the death of cells by necrosis and apoptosis.

Sonodynamic therapy initial stage used the same agents of light sensitization hemedonin and its byproducts produced for PDT. A perfectly working PS ought to be selectively absorbed and kept in the cancer cells for the treatment destroys tumor cells and create negligible harm in the immediate tissues. To enhance the efficiency of solid tumors treating, it is advisable that the sonosensitizer is induced within a vein earlier than the insonation has been done and not instantaneously into tumors for it to be adequately localized all over the tumor.

Sonodynamic treatment causes cell death in tumor cell plasma and culture and restrict neoplasm development. The effectiveness pf sonodynamic therapy also help in the treatment

of deeply situated neoplasm, together with those of the central nervous structure [66]. studies have indicated the therapy leads to mediated cancer cell death caused by destruction of ultrastructure of cancer cells, mitochondrial swelling, damage of cell membrane, and chromatic condensation. Combining sonodynamic and photodynamic therapies create a harmonious result in solid malignant tissues and post-treatment neoplasm mortification restricting the growth of neoplasm and enhancing the rate of survival. The administration of sonodynamic therapy should be done in a way that it has low sensitivity to light to reduce cutaneous side effects. Data from different studies assert the application of a treatment of various therapies for additional enhancement of bio-results and therefore minimize neoplasm development and magnitude. Fractional process also minimizes the heating effects of treatment [67]. The application of sonosensitizers together with ultrasound contrast agents result to improved sonodynamic treatment [68]. The collective factor is referred to as a theranostic agent since the introduction of the microbubble that has been

loaded in to the neoplasm cardiovascular system can be observed through ultrasound imaging, and after it have been spotted in the neoplasm via the use of ultrasound, sonodynamic treatment can be administered. A medical care-diagnostic protocol is introduced and can be used check the effectiveness of treatment. The insonation of the ultrasound contrast factor might result to more vital internal thermal bio-results like tumor vasculature, damage of the endothelial cell lining and reduced tumor vascularity.

Discussion

In the field of HNC, the treatments using PDT and surgery shows similar therapeutic results for small lesions. PDT is highly recommended for conventional treatment due to the use of second generation Ps. However, for thin lesions in HNC, oral microsurgical removal is often preferred than the use of PDT in part because of the cost of mTHPC-PDT treatment. Ultrasound therapy and diagnostic play key role in the scientific and clinical context. Sonodynamic therapy is among of the greatest innovative treatment against HNC and has a large ability to do more in the future. Molecular alteration is only experienced in cases both sensitizers and stimulus that are non-toxic are combined instantaneously reducing negative results in comparison with other conservative medical care.

Conclusion

Based on this review, it can be seen that PDT takes a major ground in the treatment of HNC, either as part of a multimodal procedure or as a single channel for treatment of diseases detected at their first stages, salvage treatment or palliative care. The discovery of new and improved PSs and nano based formulations helps in the overcoming of present limitations. Combined with improved procedures, better equipment, and enhanced dosimetry, PDT can become an improved choice for conservative treatment. PDT can be considered to be specifically suited for HNC since it has a reputable cosmetic result. Research that has been conducted recently have indicated that PDT is a safe and effective method for the treatment of head and neck cancer due to the recent enhanced efficacy and specificity of photosensitizers. Time of treatment is highly minimized whereas the depth of cancer mortification is highly amplified. Enhancement in the system of light delivery and the implementation of intra-structural therapy into PDT has enhanced the application of PDT from superficial, surface neoplasm to those that are deeply located large tumors. PDT have proven to be a unique therapeutic option to the treatment and nursing of the integrated head and neck cancer. The application of low-intensity ultrasound is believed to be non-toxic, tolerable, require use of cheap equipment, and can be easily used cancer treatment. Sonodynamic therapy uses mild-intensity ultrasound producing side effects that leads to the damage of malignant tissues. It is likely that more than one side effects result in the efficiency of a treatment, despite the significance of inertial cavitation and thermal bio-effect found in animal neoplasm experiment. In other cases, the availability of neoplasm is a disadvantage since the tumor tissues might be adjoining with a bone or a gas holding structure and not easily accessed by the ultrasound illumination. In such medical occurrences, this problem can be solved by the application of intra cavity transducers for treatment and imaging. Additionally, the present microbubble design has a restricted loading capacity to distribute therapeutic elements and the expected amount of dose. These backdrops can be eliminated by use of an enhanced microbubble design so that they can hold larger payloads.

Funding

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