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Sonodynamic therapy and common head and neck cancers: *in vitro* and *in vivo* studies

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Abstract. – Carcinogenesis is a complex multi-stage process associated with abnormal oncogenic signals in various signaling pathways. HNSCC (Head and neck squamous cell carcinoma) includes the majority of head and neck cancers (HNC). Also, HNSCC indicates a tumors heterogeneous group that derives from the squamous epithelium of the oropharynx, hypopharynx, oral cavity, and larynx. The main cancer management approach contains chemotherapy, radiation, and surgery separately or in combination. Each therapeutic approach has a limitation that influences cancer therapy procedures. Different treatment manners, stimuli-responsive therapeutic methods can improve on-target responses and reduce side effects. Sonodynamic therapy (ST) shows promising potential as an alternative treatment for cancer in the last few years. There is a hypothesis that shows ST using sonosenitizer in combination with low-intensity ultrasound (LIUS) could be useful in all kinds of cancer without focusing on specific target proteins, molecules, and/or genes. This review study discussed the application of ST for the treatment, ST mechanisms, and also, advances in the treatment of HNCs approaches in the recent decades.

Key Words:
Sonodynamic therapy, Head, Neck, Cancers.

Introduction

Carcinogenesis is a complex multi-stage process in different signaling pathway[1]. There was a hypothesis that the incidence of cancer increase with the rise of age but over the past years, abundant reports have indicated oral cancer (OC) in young[2]. The oral cavity includes form lips to the Faucial Arch (anterior surface) that is the uppermost part of the Aerodigestive tract. It is lined by squamous cell epithelium with dispersed minor salivary glands. The cavity may be divided into 5 parts: tongue, mouth floor, Buccal mucosa, maxillary/mandibular gingiva containing hard palate, and Retromolar Trigone[3-5]. OC emerges on the lip or oral cavity that is a malignant Neoplasia[6]. Seven subsites of the oral cavity are also categorized as the OC (lips, mouth floor, tongue, alveolar, Retromolar Trigone, Buccal, hard palate, and soft palate). Oral cavity cancer is usually established as OSCC (oral squamous cell carcinoma), due to the originated in the squamous cells in 90% of dental area cancers[6]. Furthermore, oral cavity cancers are broadly widespread in developing countries more than in other developed countries[7]. Other malignant cancers can arise from the lymphoid tissue, epithelium, minor salivary glands, connective tissue, and melanocytes or metastasis from a distant tumor[8,9]. About 10% of other oral cavity tumors contain sarcomas, malignant odontogenic tumors, minor salivary gland malignancies, lymphoma, and melanoma[10]. The risk factors of these types of cancers containing smoking, tobacco and betel nut chewing, poor nutrition, alcohol, and mate drinking, poor oral hygiene, and mouthwashes including a high concentration of alcohol.

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Other risk factors contain chronic trauma, HPV virus, suppression of immune system, gender, age, and genetic factors[11]. Lack of awareness and delay in diagnosis cause advanced stage of cancers. Also, inadequate knowledge of patients and physicians add to poor prognosis and decrease survival rates.

Substantial technical advances in OC treatment[2], as a lethal disorder, has a reputation, because approximately 50% of people treated for invasive cancers (except carcinoma in situ) expire from cancer and the survival rate in developing countries is less than in other countries[12,13]. Incidence and prevalence of OC are crucially correlated with distribution across various parts of the world and different geographic variation[14]. HNC is known as the sixth most common malignancy[15,16]. As most recently available analysis about 350000 (nearly 2% of all malignancies) cases of lip and oral cavity, cancer diagnosed and approximately 93000 (nearly 0.5% of all malignancies) oropharynx cancer cases were contained in 2018. The global OC epidemiological trend is altered over the years. Overall, Asia has the highest burden of OC compare to other continents and elevated prevalence in women is more significant than men[14]. Also, OC is the third most common cancer type in Asia[15,16] due to various cultural habits like alcohol drinking, tobacco chewing, and betel-quid extreme use which are considered as important risk factors that cause oral cavity cancer. Since 1990 total OSCC reported cases have elevated about 30% in Europe[17] and the estimated total OSCC reported cases are about 47000 which is nearly 1.2 % of all of the malignancies reported in the USA[14]. Sarcomas have been known as a heterogeneous group that is derived from primitive mesenchymal cells. Sarcomas originate from muscles and tissues such as connective tissue, vascular tissue, and supportive tissue[18]. Also, sarcomas comprise less than 1% of adult cancers and about 20% of malignant solid tumors in youth, adolescents, and children[19]. Many malignant diseases are also named Leukemia that emerges with an enhanced number of leukocytes in the bone marrow and/or the blood[20]. Leukemias may exhibit at all ages but different forms have various age distributions[21]. Surgery, radiation, and chemotherapy are also used as approaches to cancer management either alone or in combination[2]. New cancer therapeutic method's purposes are achieving improvement, control of locoregional, survival progression, and decreased disease recurrence. In choosing appropriate treatment, some factors like the accessibility of advanced facilities, expert's availability, cosmetic outcomes, and control of disease should be regarded[22]. Some of the new cancer treatments are ST, gene therapy, photodynamic therapy (PDT), nano theranostics, and yoga. This review study investigated the ST application for HNC treatment, ST mechanisms and also, advances in the treatment of cancers with new methods in the recent decades (2010-2020).

Cancers

Multicellular living suffers from cancers for more than 200 million years, and evidence indicates cancers among humans for more than a million years. On the contrary, infectious disorders, parasites, and several diseases are related to the environment, cancer is not mainly caused by the entity from foreign of our bodies. Destruction agents of cancers are cells of humans that have been recruited and have slipped their reins. In addition, to some extent transformed into pathological organisms and tumors arisen[3-5].

OSCC

HNC has been known as the 6th most common malignancy with nearly 600,000 new cases per year around the world[23,24]. HNSCC contains the majority of HNC, and shows a heterogeneous group of tumors that grow from the squamous epithelium of the oral cavity, oropharynx, larynx, and hypopharynx. One of the most common malignancies is oral cavity cancer[25] and oropharyngeal cancers involve nearly 4% of cancers[26] particularly in developed countries[27]. OC is malignant neoplasia that arises on the oral cavity or lips. Oral cavity cancer is frequently defined as an OSCC, due to the originated in the squamous cells in 90% of dental area cancers[1,6]. The most common OCs are tongue carcinomas which are overwhelmed 40% of OCs[28]. Different premalignant lesions are correlated with SCC development[8]. These lesions containing oral lichen planus (more common), erythroplakia, oral submucous fibrosis (with malignant transformation potential), leukoplakia[29].

Soft Tissue Sarcomas (STS)

STS are heterogeneous mesenchymal neoplasms with about 70 histological subtypes, while STS is rare[30]. There are many environmental risk factors and known genetic syndromes although the etiology of most STS is not clarified[31]. Environmental factors are (such as ionizing radiation

to patients with a radiotherapy history) or chemical exhibitors (as the vinyl chloride) identified to promote sarcoma[32-34]. The lack of an appropriate method for determining the time trend sarcomas from carcinomas is the reason for variation in reported incidence and can involve a diversity of localizations. Accordingly, about one-third of sarcomas are misclassified at primary diagnosis[35]. STS diagnosis requires professional analysis and also is difficult. World Health Organization) WHO) classified sarcoma based on the determination of cell line reached[36]. One of the supportive treatments of localized STS (in 90% of cases at diagnosis) is surgery which affects local control and survival[37].

Leukemia

Leukemias are a type of malignant disorder of the bone marrow and blood which are threatening life[20]. Generally, leukemia could be lymphoid lineages or myeloid, and also is categorized as chronic or acute. Chronic leukemia affects more mature cells which are rare in pediatric patients. Acute leukemia typically occurs in patients of every age and if the patients left the treatment, acute leukemia can become fatal[38]. Environmental irradiation and solvents are seldom found as leading factors for leukemia. Nevertheless, acute myeloid leukemia (AML) can progress as a result of DNA damaging therapy for a previous malignant disease or as a complication to an earlier diagnosed hematologic malignancy[39]. Patients who suffer from AML will initially present in numerous ways. Some cases may indicate symptomatic complications (such as infection, disseminated intravascular coagulation, or bleeding) of disease while others will be discovered on routine blood work. Examination of bone marrow is useful in determining the diagnosis and obtaining tissue for analysis to better recognize of AML subtype and severity of prognostic[40]. Also, life-threatening problems and complications of AML show the necessity of leukemia treatment. Delays in leukemia diagnosis related to physicians show the contribution of poor outcomes and increased mortality which are correlated with the disease in low-income countries[41].

Sonodynamic Therapy

Cancer has threatened the life of humans, and therapeutics approaches require widespread researches. Therefore, more researchers attract to work on cancer therapy[42]. Due to the main of abundant cancers, the search for anticancer therapy has provided several various clinical potions over the past century. Surgery, chemotherapy, radiotherapy, and a combination of these are most treatments for malignant tumors. Although combination therapy is supposed to be a prospective additive benefits[43]. However, each type of treatment manner has limitations that make various difficulties in cancer therapy. The surgery method has complications on complete clearance of cancer cells and is not an appropriate method for curing the metastasized cancer. Radiotherapy and chemotherapy may decrease tumor cells widely, but these methods will damage normal cells and tissues concurrently. Furthermore, tumor cells utilize tolerance through the long period of radiotherapy and chemotherapy. Immunotherapy can be an efficient approach on tumors but it can be expensive and probable to make a cytokine storm[42].

Stimuli-Responsive Therapeutic Approaches

In contrast to common treatments, stimuli-responsive therapeutic approaches can reduce adverse effects and improve on-target responses[44]. Recently, light as a non-invasive therapeutic with certain chemical agents as photosensitizers in photodynamic therapy (PDT) which is established as an approach of treatment and can be obtaining extensive usage in many tumors treatment[45,46]. Lower penetration of light, which is required for sensitizer activation into deep tumor sites and side effects in the tissues after treatment with PDT, are notable limitations of PDT. To overwhelmed the PDT disadvantages, ST (involves low-intensity ultrasound (LIUS)) with sonosensitizers has developed as a promising cancer treatment from the late 1980s[47].

The Difference Between ST and PDT

The significant difference between PDT and ST is the source of energy that is used to activate the sensitizers (LIUS). PDT is inefficient for deep-seated cancer treatment because of the short penetration depth of light48. Nevertheless, the major benefit of ST over PDT is that US (Ultrasound) is firmly focused on soft tissue with great penetration[49].

Mechanism of Action of Sonodynamic Therapy

The US is a mechanical sound wave (16-20 kHz). The US may be focused accurately on the cancer site to reach activation of targeted sono-

sensitizers. Also, the US kills cancer cells selectively that can be achieved without destructive effects on healthy parts of organs. Scientific evidence of ST-induced toxicity includes ROS generation through the combination of LIUS, O2, and sonosensitizers, while US/sonosensitizers are non-toxic[50]. Sonication parameters in ST (frequently 1.0-2.0 MHz at a strength of 0.5-3.0 W/cm2) are chosen to make cavitation in a tumor or a cell culture[42]. Several sensitizers initially used in ST-based studies show porphyrin-based molecules that had been utilized as photosensitizers and these involved Photofrin and hematoporphyrin (Hp), which is used in clinical PDT[51]. Porphyrin analogs, such as 4-methyl phenyl porphyrin, protoporphyrin IX (PpIX), and hematoporphyrin monomethyl ether (HMME), have collected substantial attention in ST[52]. The sonosensitizer has become a key part of recent investigations for cancer therapy, due to the mechanism of ST-mediated cell death. The US may cause cavitation when it has interacted with an aqueous environment. Cavitation includes nucleation, growth, and gas bubbles collapse under suitable circumstances. The occurrence can be categorized into inertial cavitation and stable cavitation. As compared, inertial cavitation contains gas-bubbles growth to the size of resonance, to extreme size before crumpling severely[53]. Many ROS production mechanisms in ST involved pyrolysis, ROS production, sonoluminescence, through the cavitation bubbles collapse, and ROS independent cytotoxicity is identified[50]. ROS production in ST is explained with two fundamental mechanisms here. "Sonoluminescence" is the first mechanism which is the light emission from cavitated bubbles when US radiation stimulates cavitation nearby the tumor cells surface[54]. The emission of light in saline solutions suggested that sonoluminescence can trigger sonosensitizers (i.e. Hp) in a similar pathway of PDT[42] (Figure 1). "Pyrolysis" has been known as the second mechanism of ROS production. It is suggested the temperature raising ruptures apart the material of sonosensitizer to yield radical species during inertial cavitation[53]. Several studies have established that ST can generate direct cytotoxicity in cancer cells by the production of a large amount of intracellular ROS (Table I). Currently, some evidence indicated that ST carries the alteration impacts on the microenvironment of cancer, for instance, the stimulation effect on the cancer immunity and suppression influence on cancer vasculature, which stop the cancers development[42]. ST, also with or without another treatment manner including PDT, immunotherapy, chemotherapy, and photothermal therapy is considered to accomplish a synergistic therapeutic outcome for cancers *in vivo* and *vitro*[53].

Conclusions

In recent decades, ST has been known as an alternative treatment. In theory, ST using LIUS with a sonosensitizer might be efficient in cancers without targeting specific proteins and/or genes, and molecules. ST is comprised of different components, US, molecular oxygen, and sensitizing agents which are safe individually. Possibly, ST can mediate toxicity by ROS generation, which is correlated with membrane lipids peroxidation (by peroxyl and/or alkoxyl radicals). *in vitro* and *in vivo* evidence elucidated ST efficiency in therapeutic approaches of cancer treatment[55]. Considerable penetration to tissues of US-made ST an alternative method for non-invasive cancer treatment. However, after ST is accepted as a replacement for common cancer treatments or an adjuvant, more requirements should be provided. Moreover, ST in combination with other treatment methods indicated unexpected synergistic therapeutic effects on cancer[56]. Also, nanocarriers demonstrated many benefits for tumor-targeted delivery of ST and other treatment manners and sonosensitizers[42]. Various sonosensitizers (cyanines, por-

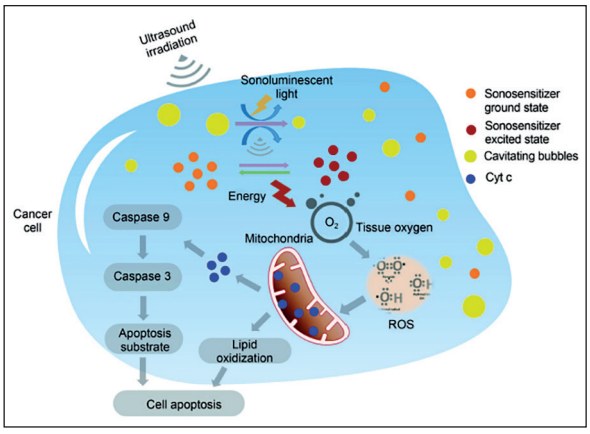

Figure 1. ST possible mechanisms. US radiation stimulates the different cavitations on the external of tumor cells. Sonosensitizer is stimulated from the ground and the produced energy may be transported to the oxygen to release ROS that causes the cell apoptosis[42].

Table I. Studies on the cancers treatment using ST.

Cancer type	Method	Outcomes	Year/Ref
OSCC	Investigation of PpIX based ST (PpIX-ST) on SAS cells. (*in vitro*/*in vivo* studies)	SAS cells via stimulating the extrinsic Fas-mediated membrane receptor pathway and arresting cell cycle to prompt apoptosis.	2017/[57]
Human leukemia/ K562 cells	Investigation of apoptosis in human l eukemia/K562 cells induced by PpIX-ST.	PpIX-ST induces apoptosis on K562 cells which involved intracellular ROS.	2014/[58]
Sarcoma 180 (S180) cells	Sonodynamic antitumor effect of PpIX in comparison with Hp (5 mg/kg) on S180 cells and investigation of the potential cell damage mechanism. (*in vivo* study)	PpIX have more potential cytotoxicity than Hp while irradiated with US	2007/[59]
SAS cells	Evaluate cell cycle phase on the SAS cells sensitivity to ST using LIUS/5 aminolevulinic acid (ALA). (*in vitro* study)	Cells in The G2/M and S phases make more intracellular PpIX, and also, have higher levels of cyclin A, and increase sensi¬tivity of ST induced cytotoxicity.	2015/[60]
Human tongue squamous carcinoma SAS	Anti-tumor effects of ST using LIUS plus ALA (*in vitro in vivo*/studies)	ALA-LIUS therapy significantly suppressed the SAS cells proliferation.	2012/[61]
S180 cells	Investigation of differences between endo-PpIX and exo-PpIX (endogenous and exogenous PpIX) in sonodynamic efficacy, pharmacokinetics, and sub-cellular localizations	Endo- and exo-PpIX in S180 cells has differences in sub-cellular localizations, and pharmacokinetics which may affect their ST efficacy and mechanisms of stimulating cell death.	2010/[62]
Human leukemia/K562 cells	Investigation of apoptosis rate and a utophagy after PpIX-ST treatment as well as the correlation between PpIX and ST.	Autophagy may be cytoprotective in the experimental system, and the ROS caused by PpIX-ST treatment may play a key role in inducing autophagy and apoptosis.	2015/[63]
HL-60 cells	Investigation of induced-apoptosis by PpIX-ST.	PpIX-ST could induce apoptosis on HL-60 cells, suggesting that apoptosis is a crucial mechanism of induced-death of cells by PpIX-ST.	2016/[64]
S180 cells	Evaluate the possible biological mechanism of cell induced-apoptosis by US activating PpIX	Oxygen free radicals show the importance in the membrane lipid peroxidation improvement, degrading phospholipids to produce FFAs, and decreasing the functional key antioxidant enzymes.	2008/[65]
Murine leukemia L1210 cells	Investigation of sonodynamic effect, sublocation, , and accumulation of Hp and PpIX	significant differences between Hp and PpIX related to the intracellular accumulation features. PpIX-ST produced more cytotoxic effect than Hp-ST.	2010/[51]
Human Leukemia U937 cells	Identify the cytotoxic effects of US-activated PpIX	Fatal induced-damage by PpIX-ST in U937 cells, and the intracellular ROS was involved during this process.	2014/[58]
S180 cells	The killing effect on S180 cells by using the combination of PpIX and focused US at the frequency of 2.2 MHz and different strengths.	PpIX alone has no significant effect on S180 cells. US alone and US combined with PPIX groups have anti-tumor effect	2007/[59]
Murine leukemia L1210 cells	Evaluation of the autophagic and apoptotic response to ST (*in vitro* study)	In L1210 cells, both apoptosis and autophagy were involved in cell induced-damage by ST.	2011/[66]

Continued

Table I *(Continued)*. Studies on the cancers treatment using ST.

Cancer type	Method	Outcomes	Year/Ref
SAS cells	The investigatation of induced-apoptosis SAS cells pulsed 1.05MHz US in combination with ALA.(*in vitro* study)	ALA-ST produced strong apoptotic effects on SAS cells	2011/[67]
Murine leukemia L1210 cells	Examination of apoptotic and autophagic responses to PpIX-ST.	ROS play a key role in starting autophagy. The sono-damaged mitochondria is enclosed by autophagic vacuoles.	2013/[68]
S180 cells	Evaluate enhancement of the apoptosis in S180 cells by US/PpIX and related biologic mechanism.	PpIX-ST could exert triggering apoptosis (antitumor effect) in S180 cells by a pathway of Fas-mediated signal transduction.	2008/[69]
Mice bearing S180 solid tumors	The sonodynamically induced antitumor effect of PpIX	US antitumor effect is increased in the occurrence of PpIX which is involved in a sonochemical mechanism.	2007/[70]
Human chronic myelogenous leukemia/K562 cells	Examine the rate of autophagy after treatment by PpIX-ST and the connection of PpIX-ST with apoptosis.	ST significantly induced K562 cells autophagy, maybe to protect K562 cells from sono-damage.	2015/[71]
K562/DOX cells	Evaluate the administration efficacy of doxorubicin (DOX) in combination with PpIX-LIUS as a potential strategy in cancer therapy.	PpIX-US could elevate the susceptibility of tumors to antineoplastic drugs.	2015/[72]
S180 cells	Examine the possible participation of mitochondria-caspase signaling pathway in ST-induced apoptosis. (*in vitro* study)	ST- and US-induced apoptosis activated mitochondria-caspase signaling pathway in S180 cells. Hp remarkably enhances the cytotoxic effect of US treatment and facilitate the apoptosis process. Singlet oxygen has effects on apoptotic signaling pathway activation and the mitochondrial damage.	2010/[73]
SAS cells	Potential using LIUS to decrease the scutellarin dosage in control, US-alone, scutellarin-alone, and combined US-scutellarin treatment groups. (*in vitro*/*in vivo* studies)	The combined treatment indicates strong anticancer effects. LIUS is increasing the scutellarin permeability into cancer cells.	2013/[74]
Human oral squamous cell line HSC-2	High intensity focused ultrasound (HIFU)/photocatalytic TiO2 nanoparticles were studied on human oral squamous cell line HSC-2. (*in vitro* study)	Cytotoxic effect of TiO2 or HIFU alone were significantly lower than HIFU+TiO2. Substantial tissue damage and necrosis in HIFU and HIFU+TiO2.	2016/[75]
OSCC	Nano engineered MSCs are advanced as a super sonosensitizer for developing nondestructive ST against OSCC. (*in vitro*/*in vivo* studies)	Stimulate tumor cell death in hypoxic conditions. LPV/M/O2 indicate the penetration tumor accumulation and tumor accumulation under US, and also, proficiently makes cancer abrogation and inhibition.	2020/[76]
OSCC	Designed the targeting OSCC with multi-functional nano-medicines to overwhelm the therapeutic obstacles during OSCC treatments, including radiotherapy, chemotherapy, and the traumatic surgery. (*in vitro*/*in vivo* studies)	Induction of the OSCC cell death. Tumor cells/xenografts have been proficiently eliminated, achieving the specific target and synergetic treatment manner against the OSCC.	2020/[77]

phyrin analogs, hybrid materials, and porphyrin analogs) have been examined for ST. Organic materials have considerable biodegradability, and they play a pivotal role in progressing the improvement of cancer therapeutics with promising application in clinics. Findings show that ST exerts inhibitory effects on the development of cancer by mitigating the microenvironment of the tumor, but the modulation mechanisms are unknown yet[42]. However, increasing data of experiments and sensitizers would entail the widespread ST application in different cancer *in vivo* models in future studies.

Future Direction

Future challenges of ST are also related to the technique including knowledge spreading and effective manners to control cavitation. Understanding the interaction between cavitation and sonosensitizers will adapt cavitation generation to improve the results while preventing wasting energy. Monitoring techniques of cavitation should be developed and applied in combination with the knowledge of sonosensitizers interactions with cavitation to control effects. Better awareness of ROS generation mechanisms will provide more efficient sonosensitizers and facilitate therapeutic response and control of US dosimetry. Methods to improve oxygenation of the tumor during ST will also have clear advantages because oxygen is essential for ROS generation. Most ST studies suggest that cancer treatment methods are spreading and ST has promising application in therapeutic approaches to cancer.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethical Approval

This article is a review and does not contain any experiment on humans or animals performed by any of the authors.

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