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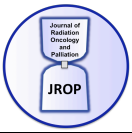

CASE REPORT **Open Access**

Low dose radiotherapy after the sonodynamic and photodynamic therapy with spirulina for relapsed cancer treatment: With literature review and three case reports

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ABSTRACT

In metastatic and advanced stage cancer patients, surgery chemotherapy (CT) or radiotherapy (RT) can not be performed because their poor performances. For this reason, local therapies have been developed that will not suppress the immune system.

CASE REPORT: *In this study was evaluated to, sonodynamic photodynamic therapy (SPDT) with low dose salvage RT was performed to three patients with the diagnosis of recurrent esophageal, vulvar and gastric cancer who applied to first RT 5 months to 1 years ago. Spinulina that photosensitizer (PS) and sonosensitizer agent were given orally. Sonodynamic therapy (SDT) with 1.5 watt/cm^2 energy of ultrasound waves with the photons of diode laser that a 650 nm wave length (PDT) (Combine name is SPDT) were applicated concurrent with spirulina before RT. Local external RT was applied 20Gy with using Helical Arc Radiation Therapy (HIART) of Tomotherapy Machine.*

RESULTS: *The 25% partiel response was obtained after 20Gy of external RT in first patient. At 20 Gy in the second patient, there was a partiel response of 85% in the subcutane nodules on above abdomen. In the third patient, a complete response was obtained at 20 Gy in the recurrent vulvar tumor. There were no any toxicity in all three patients.*

DISCUSSION: *Low dose RT after the SPDT with spirulina may be a safe and effective method for cancer patients especially which in poor performances.*

KEYWORDS: *spirulina, PDT, SDT, SPDT, photodynamic therapy, sonodynamic therapy, taloporfin, temoporfin*

ÖZET

Metastatik ve ileri evre kanserde, cerrahi kemoterapi (KT) veya radyoterapi (RT,) hastaların kötü performansları nedeni ile gerçekleştirilemez. Bu nedenle performansı ve bağışıklık sistemini baskılamayacak lokal tedaviler geliştirilmiştir.

OLGU SUNUMU*: Bu çalışmada, 5 ay ila 1 yıl önce uygulanmış olan 1.cil RT sonrasında nüks etmiş olan özofagus, vulvar ve mide kanseri tanılı üç hastaya uygulanan sonodinamik (SDT) fotodinamik (PDT) tedavi (SPDT) sonrası düşük dozlu kurtarma RT sonuçları irdelenmiştir. Işığa duyarlılaştırıcı ve sonosensitizör ajan olarak oral yoldan verilen spinulina ve 1.5 watt/cm^2 enerjili ultrason ses dalgaları ile sonodinamic tedavi (SDT), 650 nm dalga boyunda diyot lazer ile uygulanan fotodinamik tedavi (PDT) birlikte SPDT adı ile, eşzamanlı olarak ve RT'den once*

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uygulandı. RT lokal olarak HIART ile 20Gy uygulanmıştır.
BULGULAR: *Özofagus kanserli 1. hastada, 20Gy external RT'den sonra %25 kısmi cevap elde edildi. Mide kanserli 2. hastada 20 Gy'de, üst batındaki deri altındaki nodüllerde % 85'lik bir parsiyel cevap elde edildi. Vulvar kanserli 3. hastada, nüks tümörde 20 Gy'de tam bir cevap elde edildi.Toksisite görülmedi.*
TARTIŞMA: *Düşük doz Spirulina ile sonodinamik ve fotodinamik tedavi sonrası radyoterapi, kanser tedavisi için güvenli ve etkili bir yöntem olabilir.*
ANAHTAR KELİMELER: *spirulina, PDT, SDT, SPDT, fotodinamik terapi, sonodinamik Tedavi, taloporfin, temoporfin*
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Conflict of Interst*: There is no conflict of interest.*
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INTRODUCTION

Today, the surgery, RT, CT and immunotherapy are accepted as the mainstay of cancer treatment. Each of these treatment methods has limited use due to serious side effects. In metastatic and the case of many advanced cancer, surgery can not be performed with poor local performance. CT or RT can not be performed in severe comorbid patients with poor performance. The fact that immunotherapy is relatively expensive despite the relatively good results, and the serious side effects are the main limiting factors. If the therapies are suppressed by the immunity system, recurrence may occur after a short time. For this reason, local therapies have been developed that will not suppress the immune system or even improve it (1-3).

Photodynamic therapy (PDT) has the potential to meet many medical needs that have not yet been solved (1-7). It is a successful and clinically approved treatment modality in the treatment of non-malignant diseases. Although PDT is the first drug-device combination approved by the FDA about 20 years ago, it has not yet been used effectively and successfully. PDT consists of three main components. These are photosensitizer (PS), light and oxygen (O2). None of these are toxic by themselves. Together they initiate an important photochemical reaction. The single oxygen or free oxygen radical, referred to as the reactive product, can lead to cell death through apoptosis or necrosis by forming reticuloendothelial system (ROS) (1, 2).

The antitumor effects of PDT consist of three interrelated mechanisms. The direct cytotoxic effect on tumor cells can be antitumorally effected by initiating a strong inflammatory reaction, further damaging the tumor vasculature and increasing the systemic immunity with the death of cancer cells. Although the use of PDT with local treatments is not considered to be beneficial in metastatic disease, it can be a good alternative for metastatic disease because it can not be harmful to the immune system, even strengthening, combined with other therapies, The major disadvantages are that they cause pain during some treatment protocols and often cause excessive sensitivity to light in the skin. These side effects have also been abolished by newly developed agents (1-4).

The absorption of wavelength photons longer than 800 nm can not provide enough energy to generate oxygen in a singular state. The ideal light energy should have a high absorption peak between 600 to 800-nm (red to dark red) (5).

The penetration of light into the tissue depends on the wavelength, PS type and greenness, PS agents are green, such as chlorine, bacterioclorins and phthalocyanines, and agents with strong absorbance in dark red are more effective in tumor control. The first PS used clinically for cancer therapy was a mixture of water-soluble porphyrins, termed a purified hematoporphyrin derivative (HPD), which was later termed Photofrin.

The disadvantages are increased sensitivity to light in the skin and relatively low absorption at 630 nm. The use of red absorbance band and

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longer wave length in photophrin practice increases absorption. An important step has been taken in this regard by demonstrating that 5-aminolevulinic acid (ALA) and its esters can be administered topically or orally. ALA is actually a pro-drug that turns into protoporphyrin (6).

Photofrin can be successfully administered intraluminally or orally in the 630 nm wavelength, lung esophagus, stomach, biliary tract, bladder, brain and over tumors. ALA was found to be successful in topical, oral or intraluminal way to 635 nm wavelength skin, brain, bladder and esophagus tumors (7, 8).

While red light and infrared radiation penetrate the tissues more deeply, the depth of the blue light penetrating the tissue is very high. The region between 600 and 1200 nm is often referred to as the optical tissue window. However, photons up to 800 nm, do not have enough energy to initiate a photodynamic reaction because longer wavelengths (8).Gomer et al. showed that endothelial cells were more susceptible to PDT than smooth muscle cells or fibroblasts (9).

It is a noninvasive treatment method derived from PDT in 1989 (10), which is why PDT therapy is used only in superficial tumors. Hematoporphyrin derived agents used in PDT are also used in SDT. With SDT, cytotoxic cancer treatments can be performed with these sensitizing agents (2-5, 10-13).

The most important difference between PDT and SDT is the energy waves used. Ultrasonic sound waves are applied in SDT when ultraviolet or infrared light waves are used in PDT. Since the penetration of rays used in PDT is low, it may be useful only in the treatment of superficial tumors (14). It has been shown that ultrasound waves can be effective in deep tumors by reason of the its deeper penetration (15).

In SDT applications, ultrasonic irradiation was performed at 1.0 MHz, 1.5-3 W/cm2, 30 s. Growth of cancerous cells with SDT significantly inhibited angiogenesis and collagen accumulation. It has been shown that the combined treatment of SDT and antimetabolites significantly inhibits the proliferation of three different pancreatic cancer cell lines. O2MBs can effectively deliver O2 to the tumor microenvironment, thereby increasing the efficacy of O2-dependent treatments (16).

SDT coupled with PDT (SPDT) is a treatment with combination of SDT and PDT. The greatest advantage of this new therapy is the further reduction of side effects by using only a small amount of sensitizer that can be actuated simultaneously with both ultrasound and light (17). The low penetration capacity of the laser beam limits the use of PDT in deep tissues and large tumors (10, 11).

METHODS

Three patients who were treated in Radiation Oncology of Bezmialem University Medical Faculty were examined retrospectively. They are between 65 and 87 years of age, Eastern Cooperative Oncology Group (ECOG) performances were 3-4, (18) (Table 1).

In this study has 2 female and 1 male patients. The Nutritional Risk Scale (NRS 2002) nutrition scores were showed to moderately at risk in all patients (19).

Table 1. ECOG Performance status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Died

External RT was performed with the diagnosis of esophageal cancer in the first patient. The tumor recurred in the form of a red nodule with a

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2.5 cm diameter invading the skin after one year.

The second patient who relapsing stomach cancer has recurrent subcutaneous nodules on above abdomen. The third was a patient who planned radiation therapy with the cause of recurrent vulvar cancer.

Photodynamic and sonodynamic treatment (SPDT)

Sonodynamic therapy (SDT): Spinulina that photosensitizer and sonosensitizer agent were given orally as 2x750 mg/day and for 5 days before salvage external RT application. Ultrasound application with 1.5 watt/cm^2 energy was followed for 5 days in 20 minutes.

Photodynamic therapy (PDT): The diode laser beams were applied for 3 minutes with a 650 nm wave length laser and for 5 days after spirulina and SDT, before salvage external RT application

Radiotherapy: External local RT was applied 20Gy with using Helical Arc Radiation Therapy (HIART) HDD **(**Helical Direct Dynamic**)** of Tomotherapy Machine. (TomoTherapy Inc., Madison, WI). Treatment planning was performed utilizing the TomoTherapy VOLO (TomoTherapy Inc., Madison, WI) treatment planning workstation. A 6 MV beam was used for radiation planning of three patients.

Esophagus cancer patient was immobilized in the supine position with head and neck thermoplastic masks. Gastric cancer patient was immobilized in the supine position with apparatus of T-Board.

Vulvar cancer patient was immobilized in the supine position with apparatus of CombiFix. Planning Computed Tomographic (CT) images were acquired using a 3 mm slice thickness. MR/CT fusion was performed in order to assist locating tumor sites of three patients.

The planning target volume (PTV) margin to the gross target volume (GTV) was determined to be 3 to 7 mm according to tumor regions. External RT was applied as 20 Gy to relapsed esophageal tumor in one patient. RT was applied as 20 Gy to subcutaneous nodules of relapsed gastric cancer patient 20 Gy to relapsed vulvar tumor region of vulvar cancer patient.

Target volume coverage and maximum point dose were assessed as the volume of PTV receiving at least 95% (V95 %) and 105% (V105 %) of the prescribed dose (Figure 1). A total of 10 fractions of 20 Gy RT were applied daily for 5 days a week with 200 cGy fractions per day.

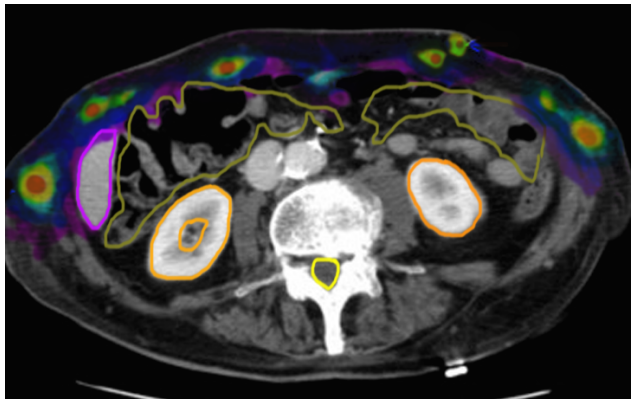

Figure 1. Radiotherapy planning isodose distribution of gastric cancer patient after SPDT

RESULTS

The 25% partiel response was obtained in the first patient who has relapsing esophageal cancer with 20Gy external RT and SPDT. At 20 Gy external RT and SPDT in the second patient who has relapsing gastric cancer. There was a reduction of 85% in the subcutane nodules on above abdomen region. In the third patient who has relapsing vulvar cancer, a complete response was obtained at 20 Gy in the recurrent tumor of her vulvar region.

DISCUSSION

Water and his group showed apoptosis and autophage formation in human leukemia cells with SDT (20). The role of intracellular calcium overload in the apoptosis of C6 glioma cells was demonstrated by SDT therapy (21). The results showed that intracellular ROS production increased. Ce6 is a second generation sonosensitizer. Ce6 is a monomeric compound. It was shown that Ce6 selectively accumulated in tumor tissues and cleared rapidly from normal

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tissues (22). The effect of Ce6-mediated SDT on human chronic myelogenous leukemia was demonstrated. When xanthine dyes such as erythrocin B and rose bengal were administered together with SDT, a good effect was obtained. Quinolone compounds were broad-spectrum antibiotics and anti-tumor effects were determined under ultrasound sonication at 2 w/cm^2 against in vitro sarcoma 180 cells (23).

Increased intracellular ROS in the non-steroidal anti-inflammatory drugs and increased intracellular ROS in the same cells showed increased cytotoxicity with ultrasonic irradiation (24).

From small molecular agents, curcumin, indocyanine green, acridine orange, hypocrin B and 5-ALA SDT have been successfully applied. Curcumin, an active component of turmeric, is a potent agent and may also be used in atherosclerosis in the future (25).

When combined with a phytochrome, hypoclidine B, ultrasound showed marked cytotoxicity on nasopharyngeal carcinoma cells and HepG2 cells (26). Hypoclidine B offers a number of advantages over other sonosensitizers, such as wide diameter welding, easy purification, low toxicity and rapid clearance.

ALA-mediated SDT showed significant apoptotic effects in squamous carcinoma (SCC) cells in human, and the mechanisms of action were explained by intracellular ROS, lipid peroxidation and mitochondrial membrane potential loss (27).

They evaluated the combined effects of SDT and PDT on breast cancer using synoporphyrin sodium (DVDMS), a newly identified sensitizer that has a synergistic effect on both SDT and PDT. SPDT caused markedly more cytotoxicity when compared to SDT or PDT alone. It did not show any significant side effects on other normal organs and tissues (28).

Salvage surgery is widely practiced in relapses after chemoradiotherapy (CRT) in esophageal cancer. However, only a few patients can be treated with high morbidity and mortality and low curative resection (29-33).

A 38-year-old patient which primary operated was treated with a new PDT modality using taloporfin sodium and a diode laser in a patient with relapse and a complete response was obtained in this patient. After 50 months, the patient was still reported as healthy (29).

Recently, Yano et al. reported a multicentric study of salvage PDT using taloporfin sodium, a second-generation photo-sensitizer for local recurrences after CRT in esophageal cancer.

The local complete response rate showed to PDT with taloporfin was 88.5%, and no skin phototoxicity was observed in the studies (34). Taloporfin and PDT are suitable for recurrent primary lesions. Taloperfin is more penetrates to muskularis and propria layer and long-term survival is expected after its use.

The most common complication after stenting is cholangitis and intra-stent tumor growth (35, 36). Stent results can be improved when treated with Photodynamic therapy with percutaneous cholangioscopy is an effective and effective method. In a study by Shim and his group median life was reported as 558 days. Cholangitis, hemobilia, side effects known as photosensitivity (37). In a study conducted by Wagner et al., In the FDT application, temoporphin was used in place of the porphyme used in other studies and the ability to penetrate twice as deep as and more cytotoxic effect was shown (38).

Spirulina, has been used in daily diets because has rich natural source of proteins, carotenoids, and other micronutrients. It could be used providing its some antiviral activity (39-44). An extract of spirulina can inhibites to herpes simplex virus type 1 and human immunodeficiency virus1 (HIV-1) infection (42-44). Spirulina also has an inhibitory effect against oral carcinogenesis. One study showed to complete response in 45% of patients treateded spirulina which used at 1 g/d. for 12 months (45).

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A study by Mishima et al (46) has shown that calcium spirulan (Ca-SP), which is a compound of spirulina, can reduces lung metastasis. Phycocyanin which active intregient of spirulina can decreases the cancer related edema and inflammation (47).

In a study with phycocyanin, an active ingredient of spirulina, and a PDT agent with selenium, 75.4% were reported. For this reason spirulina is preferred in this study. In all three cases, spirulina which has high chlorophyll, iron and protein content was considered to be a good choice because their feeding tests were moderate or bad, performances was low. Its other advantages are cost economic, easy accessibility, easy implementation characters and no side effects (39-47).

In this study, we obtained 25% response in first patients, 85% in the second and complete response in third. Since all 3 patients received the previous RT at the same site, the second dose was only 20 Gy. It is normally not possible to obtain such high response rates with such a low dose (1, 7, 30-34, 39). Spirulina is an economical, easily accessible, easily applicable agent with no side effects that can provide nutritional support and can be used in the treatment of SPDT. Studies should be done in this topic.

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