AUCTORES
Globalize your Research

Journal of General Medicine and Clinical Practice
Ron Batash *

Open Access

Review Article

The Role of Photosensitizers as Radiosensitizers in Cancer Treatment

Moshe Schaffer [1,5,θ], Ron Batash [2,*,θ], Pamella M. Schaffer [3,4], Murad Asali [5,6], Tom Zuckerman [7], Alejandro Livoff [5,7], Alfons Hofstetter [9]

[1]Dept. of Oncology, Barzilai Medical Center, Ashkelon, Israel.

[2]Orthopedic oncology unit, University hospital of Padova, Padova, Italy.

[3]Faculty of Medicin, Oradea, Romania.

[4]Dept. of Radiation Therapy, MVZ Inn Med Clinic, Oberaudorf, Germany.

[5]Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheba, Israel.

[6]Dept. of Urology, Barzilai Medical Center, Ashkelon, Israel.

[7]Dept. of Pathology, Barzilai Medical Center, Ashkelon, Israel.

[8]Sackler medical School, Tel Aviv University, Tel Aviv, Israel.

[9]Laser Center, Ludwig Maximilian University, Munich, Germany.

[θ]The first and the second authors equally contributed and considered as first authors.

***Corresponding Author:** Ron Batash, Orthopedic Oncology unit, University hospital of Padova, Padova, Italy.

Received date: March 02, 2024; Accepted date: March 11, 2024; Published date: March 26, 2024

Citation: Moshe Schaffer, Ron Batash, Pamella M. Schaffer, Murad Asali, Tom Zuckerman, et al, (2024), The Role of Photosensitizers as Radiosensitizers in Cancer Treatment, *J. General Medicine and Clinical Practice*, 7(5); **DOI:10.31579/2639-4162/155**

Abstract

Enhanced cancer resistance to treatment is associated with various mechanisms. However, cancer may frequently relapse after some time. Several strategies have emerged over the last few years to halt this process - improving cancer therapy, including - chemotherapy, radiotherapy, immunotherapy, surgery, targeted therapy, hormone therapy, stem cell transplant, and precision medicine. Among those strategies, Radiotherapy (RT) is an essential modality to treat tumors and control their growth. Tumors can withstand more ionizing radiation than normal tissue. However, the addition of radiosensitizers can adjust the effect of the radiation on tumors tissues, causing significant damage to the neoplastic tissue. PDT (photodynamic therapy) was considered a promising treatment for early and localized inoperable tumors. This work provides combination therapy comprising a radiosensitizing agent and radiation therapy, describing its effectiveness in inhibiting the proliferation of cancer cells and cancer stem cells, including mechanism of function (partially known) and the possibility of using this method as a kind of targeting therapy.

Kew Words: photosensitizers; radiosensitizers; radiotherapy; cancer therapy; cancer relapse

Introduction

New challenges in cancer therapy have emerged recently, considering enhanced resistance to conventional treatment of various cancer types. Moreover, high incidences of relapse after primary cancer regression contribute to the problem. Enhanced cancer resistance to treatment is associated with multiple mechanisms, including mutations and drug over-expression of the drug-target. Other mechanisms involve drug termination from the cells or inactivation of the drug. Several strategies have been attempted over the last few years, in order to improve cancer therapy and reduce mortality. The methods include - radiotherapy, immunotherapy, surgery, targeted therapy, hormone therapy, stem cell transplant and precision medicine. Among these strategies, Radiotherapy (RT) is an essential modality to treat tumors and hinder their growth [1-3].

As widely described in the literature, cancer lesions are comprised of a heterogeneous population of cells, which include numerous types. This may be one of the causes for failure of treatment and cancer relapse. Several cancer resistance and recurrence models have been associated with small populations of identified cancer stem cells. For instance, malignancies of hematopoietic origin and some solid cancers. Such cells are also considered cancer stem cells (CSCs) or cancer-initiating cells. These cells have self-renewal capabilities and therefore, are a fundamental concept in tumor biology4,5. Their ability to initiate tumor growth granted them the name - "tumor-initiating cells" (TICs)5. Tumor-initiating cells are phenotypically different from their fellow tumor cells, since they express explicit markers and functional features, such as resistance to conventional therapy[6-8]. TIC express organ-specific markers and characteristics that separate them from differentiated cells, e.g., expression of active DNA repair ability, expression of specific ABC drug transporters and disinclination to apoptosis signals. In clinical terms, the stem cell model for relapse may be highly suitable for

chemotherapy responding cancers with a complete response, that relapse months or years later [9,10]. One explanation for the failure of conventional cancer therapy might be the presence of CTC, reflecting the need to identify new therapies to target those cells.

Currently, there are various modalities for treating cancer, including a combination of radiation and a radio- sensitizing agent, which have been shown to enhance therapy [4,5,9-11]. Several radiosensitizers were depicted, partly in clinical use and partly experimental, such as small molecules and various chemotherapies, e.g., oxygen, oxygen mimics, hypoxia-specific cytotoxins, cisplatin, 5FU, nanoparticles, and photosensitizers. While considered high for tumors compared to normal tissue, the ability to withstand ionizing radiation can be adjusted by computer-controlled irradiation protocols with different radiation frequencies. [9,10,12-14].

Moreover, the tumor tissue selection to radiation is enhanced by radiosensitizers; which can be used to achieve a more significant rate of deterioration of the neoplastic tissue, as opposed to the additive effect of each modality [9,10]. When using radiosensitizers, one must consider two main parameters: possible complications of use and the therapeutic ratio - the likelihood of local tumor control. Most of the commonly utilized radiosensitizers are not tumor-specific and have poor selectivity. Usage of such compounds can potentially lead to severe complications as a result of their toxicity. Hence, an ongoing search for specific radiosensitizers has begun, as a means to improving the outcome of radiation therapy on relatively radio-resistant hypoxic tumor cells9,10

PDT (photodynamic therapy) was estimated to have promising results in treating early and localized inoperable tumors in the 1980s[15,16]. The technique involves a topical or systemic administration of a photosensitizer and the exposure of the tumors to a specific wavelength absorbed by the photosensitizer [15,16].

Due to their tetrapyrrolic macrocycle, the preferred photosensitizers are the porphyrins, and their equivalents, with absorption bands in the 600-800 nm wavelength (the red region of the visible spectrum) that enables high penetration into human tissue [8,16,17].

The PDT effects result from a reaction between the photosensitizer's initially formed excited singlet state and the photosensitizer's lowest triplet state, having an intersystem crossing [15-17]. Consequently, this triplet photosensitizer and the biological targets can interact with the transfer of electron or proton, generating the construction of radical particles that in turn, form oxidized products after interaction with oxygen – a process known as type I reaction[18-20].

Alternatively, the energy from the metabolite might be transferred to molecular oxygen directly, causing singlet oxygen to form. The singlet oxygen is cytotoxic, and the mechanism is called a type II reaction19. In both types of reactions, the presence of oxygen is crucial21,22. In contrast to ionizing radiation, which primarily targets cellular DNA, PDT is known to affect cellular membranes, blood vessels and mitochondria [16,23].

This paper aims to review the use of photosensitizers as selective and specific radiosensitizers. Due to the fact that there is a vast number of existing Photosensitizers, which can be used as radiosensitizers, we tried to focus mainly on main photo-radio-sensitizers. We are presenting a combination therapy technique, comprising of radiosensitizing agent and radiation therapy, which effectively inhibits the proliferation of cancer cells and cancer stem cells.

1. Photosensitiser as Radiosensitizer in Vitro and in Vivo

Photosensitizers' selectivity for tumor tissues encouraged the search for the potential use of compounds as radiosensitizers. In 1955 Schwartz et al. conducted experiments showing the radiosensitizing effects of porphyrins in patients taking HpD with radiation therapy [24,25].

The experiment showed enhanced local tumor control in patients with carcinoid tumors, fibrosarcoma, squamous cell carcinoma, and rhabdomyosarcoma [24]. In his publication, the side effects mentioned were vomiting, nausea, and remarked skin photosensitivity that lasted for several months [24]. The metabolic product is HpD, a highly heterogeneous Hp chemical derivative in a chemical reaction between acetic and sulfuric acid with hematoporphyrin. One of the partly purified forms of HpD is Photofrin II [24]. In 1960, Schwartz and Cohen demonstrated that higher doses of hematoporphyrin copper complex facilitate radioprotection, in contrast to smaller amounts, which showed a noticeable radiosensitizing effect. In 1986, Kostron et al. managed to reduce 40% of rat glioma tumor growth compared to the control group, which confirmed the radiosensitizing potential of HpD (Hemato-porphyrine derivative) [26]. One of the derivatives of perylenequinonea product of the plant Hypericum perforatum, which is used for treatment, is the red-colored Hypericin (St. John's wort) [27].

Hypericin and its derivatives have been studied for their physicochemical properties, e.g., electron transfer, singlet-oxygen sensitization, and excited-state proton transfer [28,29]. Moreover, Hypericin is an antidepressant, antiviral agent, and potent protein kinase C inhibitor, enabling tumor selectivity and specificity in photodynamic therapy [30,31]. This fact led to further studies of Hypericin as a diagnostic tool in several cancers, which induced apoptosis in tumor cells [30-33].

A study published in 2015 by Schaffer et al. [34] showed that perylenequinone derivatives (PDs) acted as potent radiosensitizers. This group proved the effects of some derivatives of Hyperecin (PDs) on tumor-initiating cells (TICs) and normal tumor cells [34]. TICs are phenotypically different from other tumor cells due to the expression of specific markers and stem functional cell characteristics, which enable resistance to conventional therapy [8,35,36]. In their study, the group checked TIC cells of PANC1 (pancreas cancer), U87 (glioblastoma), HT29 (colon cancer), MCF7 (breast cancer), A549 (lung cancer) tumor cell lines. Cells in culture were given 0.1-2M of Hypericin tetrasulfonate (HyTS), Tetrabromo hypericin (TBrHy,) or PDs Hypericin (Hy), followed by illumination with fractionated daily dose or single high dose of radiation, then, the cell viability was assessed. Additionally, the researchers assessed the tumor development of PANC1 and U87 cells in subsequently injected PDs mice and illuminated with local ionizing radiation.

Their final findings indicated that PDs expressively hindered the viability of the tumor cells exposed to radiation and grown in the TIC-enriched culture. Furthermore, TBrHy considerably stalled PANC1 and U87 tumor development in mice exposed to high levels of radiation. These findings showed that TIC viability might be used to assess radiosensitizing activity. Therefore, PDs might be considered adequate radiosensitizers, which can mark tumor cells and TICs, underlining substantial therapeutic value [34].

Photofrin II, which is made of porphyrins, synthesized by treating heorphyrin (Hp) with acid, represents one of the backbones of clinical PDT [37]. In 2001, Schaffer et al. aimed to improve the application of Photofrin II as a radiosensitizer in ionizing radiation [38,39]. In one of the studies, human cell bladder cancer (RT4) implanted mice [40] exhibited a nearly 50% reduction in tumor growth after 12 days and X-ray irradiation (5 Gy) 24 hours after injection of Photofrin II. Compared to 5-ALA, chlorin e6, Hp, and Zn-tetrasulfophtalocyanine, Photofrin II was the only photosensitizer that showed a significant change - “doubling time” of the tumor, that changed from 6.2 days to 10.9 days. However, the mechanism responsible for the positive effect remains vague due to Photofrin's heterogeneous composition. While 5-ALA with X-ray irradiation (3 Gy) was inefficient in mice with Lewis’s sarcoma tumors implanted in them, Photofrin led to a nearly 40% decrease in the tumor volume within six days. In another study, Kulka et al. [41] used Photofrin on RT4, HT-29 (colon adenocarcinoma), and U-373 MG (glioblastoma) in in-vitro survival studies. It was illuminated with X-ray (from 0 to 8 Gy (0.9 Gy min−1). A small efficacy was noticeable for two cell lines (HT4 and U-373 MG) in the following six days, in contrast to the HT-29 cell line.

These findings show the potential of Photofrin to be utilized as an efficacious radiosensitizer under certain circumstances [40] and explained the implications of the use of Photofrin [38,39].

In 2013, Benayoun et al. demonstrated the inhibition of tumor-initiating cell proliferation and enhanced efficacy of treatment in the case of glioblastoma, using a combination of PhotofrinII and ionizing radiation therapy [7]. The efficiency of hypericin as a radiosensitizer is greater than Photofrin[42]. The difference is attributed to hypericin's bio-distribution, most commonly present in the mitochondria and lysosomes [43], as opposed to Photofrin II, which is found in cell membranes [15,16,22,44]. In treating MCF-7 human breast cancer, GaPcCl was recently proven to be an efficient photosensitizer. Moreover, when combined with PDT and radiotherapy, GaPcCl demonstrated a highly effective response in cancer cells [45].

Motivating gadolinium (MGd) is classified as synthetic expanded porphyrin, which aggregates selectively in tumor cells and is responsible for the oxidation of various intracellular metabolites. MGd showed synergistic features with ionizing radiation [46]. Furthermore, radiation-induced cell killing was elevated by synthetic metalloporphyrin's [46]. Several studies [47,48] presented the benefit of photosensitizers, such as gadolinium texaphyrin (Gd-Tex) in relation to brain metastases

Various clinical examinations, including a pivotal Phase III clinical trial for the biosafety of Gd-Tex investigating the radiological, neurocognitive and neurologic progression, have been performed [47,49]. It was found that Gd-Tex was well tolerated and locally controlled in terms of radiological rate of response, neurological progression, and mortality rates related to the growth of brain tumors. Despite these promising initial results, Bernhard et al. [50] examined Gd-Tex effects on six different human tumor cell lines (SW480, HT-29, A549, U251-NCI, U-87 MG, and MCF7) and found that the radio sensitizing results were non-existent. The finding contradicted previously reported effects of Gd-Tex as a radio sensitizing factor and its potential role in radiation therapy.

Copper Cysteamine (Cu-Cy) [51] in the nanoparticles form is a novel radiosensitizer and photosensitizer that responds to light, X-ray, and microwave and emits singlet oxygen used for cancer treatment. Yet, until 2000 the killing process of Cu-Cy on cancer cells remained vague regarding colorectal cancer. Bernhard et al. examined Cu-Cy nanoparticles on SW620 colorectal cells, demonstrated efficiency, and clarified the effects' mechanisms. His findings revealed that Cu-Cy nanoparticles that have been activated by X-ray might eradicate SW620 tumor cells in a dose-dependent manner [51].

Zhipeng Liu et al. and Ghoodarzi et al. investigated the integration of gallium phthalocyanine chloride (GaPcCl)-PDT and Radachlorin-PDT with X-ray in treating MCF-7 human breast cancer cell line reported an increase in cell death compared to the use of GaPcCl-PDT without X-ray. Similarly, late apoptosis was portrayed in flow cytometry in the hybrid therapy. These results demonstrated that GaPcCl is an efficacious photosensitizer in MCF-7 human breast cancer, which concluded that combining radiotherapy and GaPcCl-PDT might be a productive strategy against cancer [45,52].

2. Mechanism of Photosensitizers as Radiosensitizer

The comprehension of the underlying mechanisms involved in tumor radiosensitization by photosensitizers is hampered because of the chemical composition of the compound, which is highly heterogeneous [16,17]. Photosensitizers (PS) become activated in 350-800 nm wavelengths. The therapeutic device (such as 12 MeV) ionizing irradiation illuminates in the wavelength of 6·10-3 to 8·10-3nm [16,17]. Regardless, X-ray devices, including the unit that was operated in the experiments described, hold a wavelength ranging 8·10-2 and 10 nm. Thus, the claim that radiosensitizing results are related to direct interaction involving the concurrent irradiation and the photosensitizers is unlikely [9,19,24,25,26].

There are a few hypotheses aimed to clarify the radiosensitization of tumors by PS: i) PS responds to cytotoxic activated molecules, e.g., hydroxyl. These radicals are the known products of the reaction of X-rays and water [10]. Schaffer et al. has demonstrated that the enhancement radiosensitizing action of PS is a possible result of hyperreactive radical derivatives [42,53]. An analogous mechanism was documented with Gd-Tex54, which underwent a reduction of a single electron and transformed into a relatively steady radical anion. The extreme anion experiences protonation in a neutral solution and has a half-life of a few hundred microseconds, leading to the formation of long-lived reactive radical particles. The solvated electron extends the hydroxyl radical lifetime by binding to it [10]. Schaffer et al. demonstrated the radio-induced degradations of cellularly-bound photofrin and radiosensitizer killing of RT4 cells by the quenching action exerted by mannitol and histidine [53]. ii) PS reduces the probable mechanisms that usually restrict radio-induced cell damage. The ionizing irradiation causes lethal and sublethal damage [10]. One hypothesis described by Schaffer et al. claims that sublethal damage might evolve into lethal damage or excite repair mechanisms. If combined with ionizing radiation, PS may reduce repair process probability[42,55].

3. Clinical Application

In spite of the various studies with different PS as selective and specific radiosensitizers, the information about their clinical applications is very scarce. The radiosensitizing effect of porphyrins was demonstrated as early as 1955. Schwartz et al. [24,25] treated patients by combining HpD with radiation therapy, which enhanced local tumor management, specifically in patients diagnosed with carcinoid tumors, squamous cell carcinoma, fibrosarcoma, and rhabdo-myosarcoma [14]. The unfavorable side effects described in this publication included nausea, vomiting, and noticeable skin photosensitivity lasting for several months [21].

Mehta et al. [56] conducted a randomized trial that included the combination of motivating gadolinium and whole-brain radiation in patients with brain metastases. Viala et al.48 conducted Phases IB and II trials that included treatment with multidose trials of gadolinium texaphyrin, a radiation sensitizer observable by MRI. Carde et al. [49]. treated patients with brain metastases by using radiation enhancers and motexafin gadolinium in in a multicenter phase Ib/II trial. A review from 2011[57] claimed that motexafin gadolinium was a novel radiosensitizer with documented effectiveness, especially in cases with brain metastases. Had this agent been used in experimentation before, in NSCLC brain metastatic patients, who had not been delayed by systemic chemotherapy treatment, it could have turned into a method of standard of care in this area. Further trials with motexafin gadolinium are ongoing and remain promising. Nevertheless, we did not find any updated literature using this substance in clinical application.

In 2006, Schaffer et al. [58] published their results describing Photofrin II as a radiosensitizing treatment in various tumors. The study's goal was to test the methodology and assess radiation therapy toxicity when combined with PhotofrinII on 18 patients in advanced stages of their disease. These patients had a few lines of chemotherapy or surgery. In all the patients, the relative serum levels of Photofrin II showed the best results in the first days successive to intravenous injection with a subsequent sudden decrease. The course of treatment with significant effects of Photofrin II (5-6 days) corresponded appropriately to the therapeutic window [59]. In terms of clinical application, a boost of irradiation was admitted, in order to gain the highest impact on tumor tissue with minimal side effects.[58] (Table 1).

Table 1. Characteristics (n=18, 26-80 years of age)

Description	Number
Locally advanced bladder carcinoma	1 female, 2 males
Local recurrence bladder carcinoma	1 male
Cervical carcinoma, FIGO IIIb	1
Locally advanced sarcoma, pelvic area	2
Astrocytoma, grade III	2
Anaplastic astrocytom grade III (recurring after irradiation)	1
Multiforme glioblasstoma (WHO grade IV	4
Base of the tongue carcinoma, recurring	1
Cholangiocarcinoma	2
Adenocarcinoma, sphenoid sinus	1

Table 1: distribution of tumor types treated with Photophrin II. [58]

Results are shown in Table 2

Table 2. Results

Complete remission

Description	No. of patients
Pelvic sarcoma, follow-up 49 months, recurrence	1
Cervical carcinoma, after 24 months, recurrence	1
Astrocytoma III, follow-up 38 months	1
Adenocarcinoma, sphenoid sinus, recurrence, follow-up 20 months	1
Cholangiocarcinoma, recurrence after 4 months	1

Partial remission

Description	No. of patients
Bladder cancer, follow-up 4, 11, 12 months	3
Glioblastoma, 1 progression after 16 months	2
Astrocytoma III, follow-up 30 months with chemotherapy	1
Sarcoma, pelvic region, follow-up 7 months, then progression	1
Cholangiocarcinoma, progression after 6 months	1

Other

Description	No. of patients
Base of the tongue carcinoma	1 – lost from control after 3 months
Bladder cancer	1 – died 3 months after treatment
Gliobastoma	1 – died after 1 month from tumor, 1 - died after 4 months from tumor
Anaplastic astrocytoma recurrence	1 – died 5 months after treatment

Table 2: impact on tumor tissues [58]

[58]. Due to the light sensibility by photosensitizers, especially photofrin II, the patients were protected from light during their treatment for a period of 3-4 weeks. All lights indoors were limited with lamps of 40W. Two of these patients with advanced tumors, one female with Astrocytoma Grade III and another female with Cervix Carcinoma FIGO IIIb, are still alive and currently free of disease [60,61].

Discussion

The literature review and demonstrated results illustrate that PS might be utilized as a radio sensitizing agent in the right circumstances. While PS on its own showed no noticeable tumor response in concentrations that presented a marked radio sensitizing effect, the radiosensitizing effect it has can be confirmed in highly radio resistant tumor models, such as bladder carcinoma and glioblastoma [34,55,58,60,61]. As a general rule, radiosensitizers imitate the effects of oxygen caused by free radicals in radiation therapy. Nitroimidazole is the most common radiosensitizer evaluated in clinical studies. A significant drawback of this agent lies in its neurotoxicity, which prevented using an effectual dose with a standard daily fractionated radiation [54,62]. Other compounds, for example, Tirapazamine[63,64], bovine hemoglobin modified with polyethylene glycol (PEG)[65], and RSR [13,66], are currently in the clinical investigation for hypoxic tumor cells.

The direct consequence of radiation (RT) is to cause double-strand breaks (DSB) and single-strand breaks (SSB) in DNA. The breaking of the DNA

leads to the termination of cell division and cell proliferation, and in some cases, to cell necrosis and cell apoptosis. See figure 1a.[24,25,26,34,38]

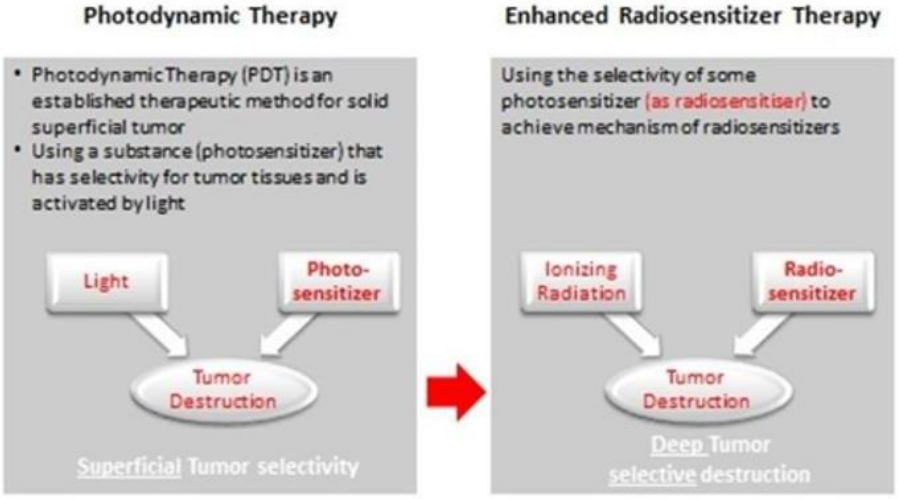

Figure 1a: mechanism of action of photodynamic therapy and radiosensitizer therapy - ROS are generated by light or photosensitizer and lead to tumor destruction.[24,25,26,34,38]

The indirect consequences of radiation lead to the generation of reactivity of Oxygen Radicals such as RO; ROS might cause cellular stress, induce biomolecules damage and eventually change the cellular signaling pathways. A number of studies demonstrated that 70% of the patients should be treated with controlled linear accelerators to carry the specific radiation quantities to the malignant tumor or the selected areas inside the tumor tissue [51,62,67,68].

Although these advanced developments increase the therapeutic results, hurdles still exist - cancer stem cells and tumor heterogeneity, limiting the use of RT alone as an ns of tumor eradication. However, by utilizing radiosensitizers that enhance the radiosensitivity of the tumor tissue and have toxicity within the range of pharmacologically normal tissue, one can apply RT more effectively and achieve the desired outcome [62,67,69].

When combined with radiation, radiosensitizers demonstrate higher tumor inactivation than predicted from the particular singular modalities [69,70]. The mechanisms of action of radiosensitizers can be classified into five different steps: (1) blocking the radioprotective effect of intracellular thiols or other endogenous substances; (2) generation of cytotoxic agents by radiosensitizer radiolysis; (3) inhibition of biomolecules repair; (4) thymine analogs incorporation into DNA; and (5) electrophilic activity of oxygen mimickers [9,70].

According to recently published studies, radiosensitizers can be categorized into three different classes, based on their molecular structure: little molecules, e.g., oxygen Mimics [5,70], macromolecules, e.g., Proteins and Peptides, and Oligonucleotides [67,68]. The last group is nanomaterials, e.g., metal and ferrite nanomaterials [69,70]. Junzhi Liu, et al. [70], found that acridine orange (AO), a small molecule radiosensitizer, can be loaded onto mMnO2 nanoparticles at very high efficiency and released to the surroundings in a controlled fashion. This review has focused on PS as radiosensitizers, which belongs to the second group. Not all commercially available PS evaluated can perform as a radiosensitizer. Furthermore, it appears to be utilized only as a photosensitizing agent [34,55].

As mentioned previously in this review, a number of hypotheses aim to showcase the PS radiosensitization of tumors: i) PS has a reaction with molecules that have been activated by cytotoxin, e.g., hydroxyl, radicals that are the products of the interaction of X-rays and water [10,41,42,49,51,56].

ii) PS reduces the chances of starting repair processes that prevent radio-induced cell damage [41,50]. The damage that Ionizing irradiation causes split into two categories62: sublethal damage and lethal damage. The sublethal damage might become lethal or excite the cell mechanisms of repair; the use of Photofrin might minimize the effects of those mechanisms if used in addition to ionizing radiation.

The radiosensitizing ability of PS is a subject of interest for several reasons, regardless of its actual course of action. PS is clinically approved in large amounts in Photodynamic Therapy of cancer. Hence, its use as a radiotherapeutic substance is derived from the ability to avoid, or at least significantly reduce expensive toxicological studies. PS has demonstrated no toxicity in humans at the doses used in radiotherapy [11,17,18,72] and showed certain selectivity of tumor targeting. This is stated in comparison to a number of radiosensitizers in clinical uses that have a much lower tumor targeting and demonstrate harsh side effects in in vivo settings [15,62].

PS's ability to be utilized as a phototherapeutic and a radiotherapeutic substance provides extraordinary insights on its mechanisms, and enables superior regulation of tumor growth.

However, various PS cause skin photosensitization (depends on the type of PS) that might hinder the use of this agent, while radiation therapy is considered. This is also true for the practice of boost irradiation, HDR following loading irradiation, brachytherapy, or only high precision radiation therapy [37-40]. The standard radiation dose in these modalities is ranged in ranges 2-16 Gy, which is administered to the tumor in a limited time and deprived of loco-regional irradiation. In vivo and vitro studies demonstrated that PS can be utilized in cases of tumor tissue hypoxia and can be considered an effectual radiosensitizer [7,37-41,55,56,73].

The combination of PS with a known contrast media - Gadolinium or with Manganese-dipyriddoxyl-5`diphosphate (Mn-DPDP – might be looked at in search of diagnostic and treatment methods [71,74].

Conclusion

We believe that PS could potentially become a symbol for helpful agents in managing tumors and demonstrate: i) Better efficacy of radiation on the tumor alone, leaving the radiation effects on the neighboring tissues unchanged. ii) Enhancement of mechanisms that hinder hypoxic cells. iii) Minor toxicity in humans.

Author contribution

Moshe Schaffer and Ron Batash– initiated the study, contributed to its conception, design and writing of the manuscript.

Pamella Schaffer and Alfons Hofstetter designed and performed part of the experiments in the review.

Alejandro Livoff, Murad Asali and Tom Zuckermann contributed to the clinical data and review of the literature.

All authors reviewed and agreed on the manuscript.

Conflict of Interest

All authors state that there are no conflicts of interest.

Acknowledgment

We wish to express our gratitude to Prof. Giulio Jori, who is considered among the leading pioneers in the field of radiosensitizers and photodynamic therapy.

References

1. Krzyszczyk P, Acevedo A, Davidoff EJ, et al. (2018). The growing role of precision and personalized medicine for cancer treatment. Technology (Singap World Sci). Sep-Dec;6(3-4):79-100.
2. Kułakowski A. (2011). The contribution of Marie Skłodowska-Curie to the development of modern oncology. Anal Bioanal Chem. Jun;400(6):1583-1586.
3. Martin OA, Martin RF. (2020). Cancer Radiotherapy: Understanding the Price of Tumor Eradication. Front Cell Dev Biol; 8:261.
4. Bernier J, Hall EJ, Giaccia A. (2004). Radiation oncology: a century of achievements. Nat Rev Cancer. Sep;4(9):737-747.
5. Baumann M, Krause M, Hill R. (2008). Exploring the role of cancer stem cells in radioresistance. Nat Rev Cancer. Jul;8(7):545-554.
6. Zhou BB, Zhang H, Damelin M, Geles KG, Grindley JC, et all., (2009). Tumour-initiating cells: challenges and opportunities for anticancer drug discovery. Nat Rev Drug Discov. Oct ;8(10):806-823.
7. Benayoun L, Gingis-Velitski S, Voloshin T, et al. (2012). Tumor-initiating cells of various tumor types exhibit differential angiogenic properties and react differently to antiangiogenic drugs. Stem Cells. Sep;30(9):1831-1841.
8. Benayoun L, Schaffer M, Bril R, et al. (2013). Porfimer-sodium (Photofrin-II) in combination with ionizing radiation inhibits tumor-initiating cell proliferation and improves glioblastoma treatment efficacy. Cancer Biol Ther. Jan;14(1):64-74.
9. Cardilin T, Almquist J, Jirstrand M, Zimmermann A, El Bawab S, et all., (2018). Model-Based Evaluation of Radiation and Radiosensitizing Agents in Oncology. CPT Pharmacometrics Syst Pharmacol. Jan;7(1):51-58.
10. Perez CA, Brady LW, Halperin EC, Schmidt-Ullrich RK. (2004). Principles and Practice of Radiation Oncology. Lippincott Williams & Wilkins.
11. Dean M, Fojo T, Bates S. (2005). Tumour stem cells and drug resistance. Nat Rev Cancer. Apr;5(4):275-284.
12. Zhang W, Anker L, Law RE, et al. (1996). Enhancement of radiosensitivity in human malignant glioma cells by hypericin in vitro. Clin Cancer Res. May 2(5):843-846.
13. Sun Y, Xu H, Tang S, Meng Y, Dong Z, et all., (2005). [Effects of hypericin associated with radiotherapy on human laryngeal squamous cell carcinoma strain Hep-2]. Lin Chuang Er Bi Yan Hou Ke Za Zhi. Dec;19(24):1127-1130.
14. Wessels JT, Busse AC, Rave-Fränk M, et al. (2008). Photosensitizing and radiosensitizing effects of hypericin on human renal carcinoma cells in vitro. Photochem Photobiol. Jan-Feb ;84(1):228-235.
15. Stewart F, Baas P, Star W. (1998). What does photodynamic therapy have to offer radiation oncologists (or their cancer patients)? Radiother Oncol. Sep;48(3):233-248.
16. Macdonald IJ, Dougherty TJ. (2001). Basic principles of photodynamic therapy. Journal of Porphyrins and Phthalocyanines;5(2):105-129.
17. Miller JW, Schmidt-Erfurth U, Sick Enberg M, et al. (1999). Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of a single treatment in a phase 1 and 2 study. Arch Ophthalmol. Sep;117(9):1161-1173.
18. Foote CS. Definition of type I and type II photosensitized oxidation. Photochem Photobiol. Nov 1991;54(5):659.
19. Xu J, Gao Jh, Wei Q. Combination of Photodynamic Therapy with Radiotherapy for Cancer Treatment. Journal of Nanomaterials. 2016; 2016:8507924.
20. Alzeibak R, Mishchenko TA, Shilyagina NY, Balalaeva IV, Vedunova MV, et all., (2021). Targeting immunogenic cancer cell death by photodynamic therapy: past, present and future. J Immunother Cancer. Jan;9(1)
21. Henderson BW, Bellnier DA. (1989). Tissue localization of photosensitizers and the mechanism of photodynamic tissue destruction. Ciba Found Symp.; 146:112-125; discussion 125-130.
22. Byrne CJ, Marshallsay LV, Ward AD. (1990). The composition of Photofrin II. J Photochem Photobiol B. Jun;6(1-2):13-27.
23. Chen B, Roskams T, de Witte PA. (2002). Antivascular tumor eradication by hypericin-mediated photodynamic therapy. Photochem Photobiol. Nov;76(5):509-513.
24. Schwartz SK, Absolon K, Vermund H. (1955). Some relationships of porphyrins, X-rays and tumors.
25. Schwartz S, Keprios M, Modelevsky J, Freyholtz H, Walters R, et all., (1978). Modification of Radiosensitivity by Porphyrins: Studies of Tumors and Other Systems. Springer Berlin Heidelberg:227-235.
26. Kostron H, Swartz MR, Miller DC, Martuza RL. (1986). The interaction of hematoporphyrin derivative, light, and ionizing radiation in a rat glioma model. Cancer. Mar 1;57(5):964-970.
27. Huang LF, Wang ZH, Chen SL. (2014). Hypericin: chemical synthesis and biosynthesis. Chin J Nat Med. Feb;12(2):81-88.
28. Darmanyan AP, Jenks WS, Eloy D, Jardon P. (1999). Quenching of Excited Triplet State Hypericin with Energy Acceptors and Donors and Acceptors of Electrons. The Journal of Physical Chemistry B;103(17):3323-3331.
29. Rahimipour S, Palivan C, Barbosa F, et al. (2003). Chemical and photochemical electron transfer of new helianthrone derivatives: aspects of their photodynamic activity. J Am Chem Soc. Feb 5;125(5):1376-1384.

30. Lavie G, Valentine F, Levin B, et al. (1989). Studies of the mechanisms of action of the antiretroviral agents hypericin and pseudohypericin. Proceedings of the National Academy of Sciences;86(15):5963-5967.

31. Delaey E, Zupko I, Chen B, et al. (2003). Comparison of hexamethylhypericin and tetrabromohypericin to hypericin for their in vivo efficacy as PDT tools. Int J Oncol. Aug;23(2):519-524.

32. Kashef N, Borghei YS, Djavid GE. (2013). Photodynamic effect of hypericin on the microorganisms and primary human fibroblasts. Photodiagnosis and Photodynamic Therapy. 10(2):150-155.

33. de Andrade GP, de Souza TFM, Cerchiaro G, Pinhal M, Ribeiro AO, et al., (2021). Hypericin in photobiological assays: An overview. Photodiagnosis Photodyn Ther. Sep; 35:102343.

34. Schaffer M, Bril R, Batash R, et al. (2015). Hypericin and its Derivatives Act as Radiosensitizing Agents That Can Inhibit Tumor Initiating Cell Viability. Clinical Cancer Drugs;2(2):119- 127.

35. Reya T, Morrison SJ, Clarke MF, Weissman IL. (2001). Stem cells, cancer, and cancer stem cells. Nature. Nov 1;414(6859):105-111.

36. Batlle E, Clevers H. (2017). Cancer stem cells revisited. Nat Med. Oct 6;23(10):1124-1134.

37. Schaffer M, Schaffer PM, Jori G, et al. (2002). Radiation therapy combined with photofrin or 5-ALA: effect on Lewis's sarcoma tumor lines implanted in mice. Preliminary results. Tumori. Sep- Oct;88(5):407-410.

38. Schaffer M, Schaffer PM, Corti L, et al. (2001). Photofrin II as an efficient radiosensitizing agent in an experimental tumor. Onkologie. Oct;24(5):482-485.

39. Schaffer M, Schaffer PM, Hofstetter A, Dühmke E, Jori G. (2002). On the double role of photofrin as a photo- and a radio-sensitising agent: a possible new combination therapy for tumours. Photochem Photobiol Sci. Jun;1(6):438-339.

40. Schaffer M, Schaffer PM, Vogesser M, et al. (2002). Application of Photofrin II as a specific radiosensitising agent in patients with bladder cancer--a report of two cases. Photochem Photobiol Sci. Sep;1(9):686-689.

41. Kulka U, Schaffer M, Siefert A, et al. (2003). Photofrin as a radiosensitizer in an in vitro cell survival assay. Biochemical and biophysical research communications;311 1:98-103.

42. Schaffer PM, Kulka U, Ertl-Wagner BB, et al. (2007). The influence of oxygen on the radiosensitizing activity of Photofrin II and hypericin. Journal of Porphyrins and Phthalocyanines; 11:736-741.

43. Ali SM, Olivo M. (2002). Bio-distribution and subcellular localization of Hypericin and its role in PDT induced apoptosis in cancer cells. Int J Oncol. Sep;21(3):531-540.

44. Reddi E, Ceccon M, Valduga G, et al. (2002). Photophysical properties and antibacterial activity of meso-substituted cationic porphyrins. Photochem Photobiol. May;75(5):462-470.

45. Mayahi S, Neshasteh-Riz A, Pornour M, Eynali S, Montazerabadi A. (2020). Investigation of combined photodynamic and radiotherapy effects of gallium phthalocyanine chloride on MCF-7 breast cancer cells. J Biol Inorg Chem. Feb;25(1):39-48.

46. O'Hara JA, Douple EB, Abrams MJ, Picker DJ, Giandomenico CM, et. all., (1989). Potentiation of radiation-induced cell kill by synthetic metalloporphyrins. Int J Radiat Oncol Biol Phys. Apr;16(4):1049-1052.

47. Evens AM, Balasubramanian L, Gordon LI. (2005). Motexafin gadolinium induces oxidative stress and apoptosis in hematologic malignancies. Curr Treat Options Oncol. Jul;6(4):289-296.

48. Viala J, Vanel D, Meingan P, Lartigau E, Carde P, et all., (1999). Phases IB and II multidose trial of gadolinium texaphyrin, a radiation sensitizer detectable at MR imaging: preliminary results in brain metastases. Radiology. Sep;212(3):755- 759.

49. Carde P, Timmerman R, Mehta MP, et al. (2001). Multicenter phase Ib/II trial of the radiation enhancer motexafin gadolinium in patients with brain metastases. J Clin Oncol. Apr ;19(7):2074-2083.

50. Bernhard EJ, Mitchell JB, Deen D, Cardell M, Rosenthal DI, et all., (2000). Re-evaluating gadolinium (III) texaphyrin as a radiosensitizing agent. Cancer Res. Jan 1;60(1):86-91.

51. Liu Z, Xiong L, Ouyang G, et al. (2017). Investigation of Copper Cysteamine Nanoparticles as a New Type of Radiosensitiers for Colorectal Carcinoma Treatment. Sci Rep. Aug 24;7(1):9290.

52. Ghoodarzi R, Changizi V, Montazerabadi AR, Eyvazzadaeh N. (2016). Assessing of integration of ionizing radiation with Radachlorin- PDT oan MCF-7 breast cancer cell treatment. Lasers Med Sci. Feb;31(2):213-219.

53. Schaffer M, Kulka U, Schaffer PM, et al. (2006). The role of radical derivatives of high reactivity in the radiosensitizing action of Photofrin II. Journal of Porphyrins and Phthalocyanines; 10:1398-1402.

54. Young SW, Qing F, Harriman A, et al. (1996). Gadolinium (III) texaphyrin: a tumor selective radiation sensitizer that is detectable by MRI. Proc Natl Acad Sci U S A. Jun 25;93(13):6610-6615.

55. Schaffer M, Schaffer PM, Corti L, et al. (2002). Photofrin as a specific radiosensitizing agent for tumors: studies in comparison to other porphyrins, in an experimental in vivo model. J Photochem Photobiol B. Apr;66(3):157-164.

56. Mehta MP, Shapiro WR, Glantz MJ, et al. (2002). Lead-in phase to randomized trial of motexafin gadolinium and whole-brain radiation for patients with brain metastases: centralized assessment of magnetic resonance imaging, neurocognitive, and neurologic end points. J Clin Oncol. Aug 15;20(16):3445- 3453.

57. Thomas SR, Khuntia D. (2011). Motexafin gadolinium: a promising radiation sensitizer in brain metastasis. Expert Opin Drug Discov. Feb;6(2):195-203.

58. Schaffer M, Ertl-Wagner B, Schaffer PM, et al. (2006). Feasibility of photofrin II as a radiosensitizing agent in solid tumors-- preliminary results. Onkologie. Nov;29(11):514-519.

59. Vogeser M, Schaffer M, Egeler E, Spöhrer U. (2005). Development of an HPLC method for monitoring of Photofrin II therapy. Clinical biochemistry;38 1:73-78.

60. Schaffer M, Hofstetter A, Ertl-Wagner B, Batash R, Pöschl J, et all., (2013). Treatment of astrocytoma grade III with Photofrin II as a radiosensitizer. A case reports. Strahlenther Onkol. Nov;189(11):972-976.

61. Schaffer P, Batash R, Ertl-Wagner B, Hofstetter A, Asna N, et all., (2019). Treatment of cervix carcinoma FIGO IIIb with Photofrin II as a radiosensitizer: a case report. Photochem Photobiol Sci. May 15;18(5):1275-1279.

62. Koch CJ, Parliament MB, Brown JM, Urtasun RC. (2010). 4 – Chemical Modifiers of Radiation Response: 55-68.
63. Koch CJ. (1993). Unusual oxygen concentration dependence of toxicity of SR-4233, a hypoxic cell toxin. Cancer Res. Sep 1;53(17):3992-3997.
64. Brown JM. (1993). SR 4233 (tirapazamine): a new anticancer drug exploiting hypoxia in solid tumours. Br J Cancer. Jun;67(6):1163-1170.
65. Teicher BA, Ara G, Chen Y-n, et al. (1996). PEG-Hemoglobin: Effects on tumor oxygenation and radiosensitization. Radiation Oncology Investigations;4(5):200-210.
66. Amorino GP, Lee H, Holburn GE, et al. (2001). Enhancement of tumor oxygenation and radiation response by the allosteric effector of hemoglobin, RSR13. Radiat Res. Sep;156(3):294-300.
67. Wardman P. (1973). Chemical Radiosensitizers for Use in Radiotherapy. Clinical Oncology. 2007/08/01/ 2007;19(6):397-417. Adams GE. Chemical radiosensitization of hypoxic cells. Br Med Bull. Jan;29(1):48-53.
68. Wang H, Mu X, He H, Zhang XD. (2018). Cancer Radiosensitizers. Trends Pharmacol Sci. Jan;39(1):24-48.
69. Gong L, Zhang Y, Liu C, Zhang M, Han S. (2021). Application of Radiosensitizers in Cancer Radiotherapy. Int J Nanomedicine.; 16:1083-1102.
70. Liu J, Zhang W, Kumar A, et al. (2020). Acridine Orange Encapsulated Mesoporous Manganese Dioxide Nanoparticles to Enhance Radiotherapy. Bioconjug Chem. Jan 15;31(1):82-92.
71. Rose H, Wagner H. (1965). [The effect of hypericin as a sensitizer of biological systems against visual and ionizing radiation]. Radiobiol Radiother (Berl);6(4):477-483.
72. Die Wirkung von Hypericin als Sensibilisator biologischer Systeme gegenüber optischen und ionisierenden Strahlen.
73. Schaffer M, Ertl-Wagner BB, Schaffer PM, et al. (2005). The Application of Photofrin II as a sensitizing agent for ionizing radiation--a new approach in tumor therapy? Current medicinal chemistry;12 10:1209-1215.
74. Briand Y. (1992). [Contrast agents in magnetic resonance. From gadolinum complexes to superparamagnetic spinels]. Rev Prat. Apr 1;42(7):857-861. Produits de contraste en résonance magnétique. Des complexes de gadolinium aux spinelles superparamagnétiques.

DOI:10.31579/2639-4162/155