Radiodynamic Therapy with Photosensitizers: Mini-Review of Experimental and Clinical Studies

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Abstract: Photodynamic Therapy (PDT) is a light-based method that uses photo-reactive molecules, such as different types of photosensitizers (PS), to destroy malignant tumors. As some authors testify, PS was shown to act as a radio-reactive molecule by enhancing generation of reactive oxygen species upon X-ray irradiation. The method of treatment, which is based on the combined use of PS and ionizing radiation, is called «Radiodynamic therapy» (RDT). The advantage of RDT over PDT is the X-ray's penetrability through tissues, which will find many applications for treatment of deep malignant tumors. The authors of a number of research centers in Japan, Germany, Israel and Lithuania presented the experience of using RDT in experiments on tumor cell lines and animals with transplanted tumors. A clinical approbation of the method has been started in patients with unresectable forms of bladder and cervical cancer, with gliomas and other forms of malignant tumors. The data obtained in experiments on cultures of tumor cells and animals with transplanted tumors indicate a high antitumor efficacy of the RDT with various types of PS. This fact is confirmed by a statistically significant decrease in viable tumor cells with the combined use of RT and PS, as well as a pronounced inhibition of the growth of transplanted tumors compared with the control groups, including the group of radiation therapy in mono mode. The preliminary data obtained show good tolerability of the method in clinical oncology (no serious adverse reactions) and satisfactory antitumor efficacy (an increase in the frequency of objective responses and an increase in the % reduction in tumor volume, which made it possible to transfer them to a resectable state).

Keywords: Photosensitizer, radiation therapy, radiodynamic therapy, tumor cells, transplanted tumors, clinical trials.

INTRODUCTION

Radiation therapy (RT) is one of the three main treatments for patients with malignant neoplasms. As modifiers that selectively enhance sensitivity of tumor cells to ionizing radiation, various physical and chemical effects are used: hyperbaric oxygenation, local and general hypoxia, electron-acceptor compounds, artificial hyperglycemia, local and whole-body hyperthermia, etc. The use of radiomodifiers (radiosensitizer, RS) makes it possible to increase the radiosensitivity of tumor cells located in hypoxic zones of the tumor, without increasing the degree of radiation damage to normal oxygenated cells [1].

Recently, the possibility of using PS as agents that increase the antitumor efficacy of RT has been actively studied. This area of scientific research in oncology is called «Radiodynamic therapy» (RDT) [2]. It's common knowledge that PS are irradiated with visible light, limiting treatment to relatively superficial, localized tumors. The ability of high-energy radiation to activate the PS in this method is therefore a subject of active investigation, since high-energy x-ray and gamma ray photons can penetrate deeply into tissue [3]. The main mechanisms of the antitumor response in the combined use of RT and PS have not been sufficiently studied. According to Shaffer M. *et al*., on the one hand, PS (for example, «Photofrin II»), when exposed to ionizing radiation, can enhance the radiolytic effect due to oxygen species formed in the tumor cell under the influence of radiation itself [4]. On the other hand, RT leads to sublethal and lethal damage to tumor cells. In the future, sublethal changes are usually reversible based on the mechanisms for restoring the functions of the tumor cell. In the case of activation of «Photofrin II» by ionizing radiation, the oligomeric components of this PS, interacting with intermediate free radicals (hydroxyl radicals) formed in the tumor cell during irradiation, prevent the development of these processes and, consequently, this combination creates antitumor effects [5].

Of particular interest are studies into the radiosensitizing properties of PS used in PDT. The first PS whose radiosensitizing activity was proved in

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ISSN: 1927-7210 / E-ISSN: 1927-7229/22

Table 1: Antitumor Efficacy of Radiodynamic Therapy in an *In Vitro* Experiment

Authors/ references	Country	Tumor cell culture	PS, dose	RT regimens	Antitumor efficacy
Kulka U. *et al.*, 2003 [8]	Germany	human bladder cancer RT4 colon adenocarcinoma HT-29 glioblastoma U-373MG	Photofrin II, 1 μg/ml	Muller RT 250 X-ray device, 225 kV, 15 mA, 0.35 Cu-filter, dose-rate of 0.9 Gy/min. Single focal doses 2-4-6-8 Gy	% of viable RT4 cells PS + RT 6 Gy – 4.7±2.3 vs. RT 6 Gy – 6.7±2.2 ($p<0.05$) PS + RT 8 Gy – 0.9±0.5 vs. RT 8 Gy – 1.7±0.7 ($p<0.05$) % of viable HT-29 cells PS + RT 6 Gy – 2.7±1.1 vs. RT 6 Gy – 3.9±1.1 ($p<0.05$) PS + RT 8 Gy – 0.2±0.1 vs. RT 8 Gy – 0.5±0.2 ($p<0.05$) % of viable U-373MG cells PS + RT 6 Gy – 2.7±1.1 vs. RT 6 Gy – 3.9±1.1 ($p<0.05$) PS + RT 8 Gy – 0.2±0.1 vs. RT 8 Gy – 0.5±0.2 ($p<0.05$)
Schaffer M. *et al.*, 2011 [9]	Israel	human bladder cancer RT4	Photofrin II, 2.5-5-7.5-10 μg/ml	Mueller RT 250 X-ray device radio-adaptive dose of 0.05 Gy at a dose rate of 0.03 Gy/min (225 kV, 5 mA, 0.35 mm Cu). 4 h after pre-irradiation, cells were further irradiated with 2 Gy at a dose rate of 1.0 Gy/min (225 kV, 15 mA, 0.35 mm Cu)	Pre-irradiation 0.05 Gy + PS 5 mg/kg + RT 2 Gy vs. pre-irradiation 0.05 Gy + RT 2 Gy - a decrease in the number of viable RT4 cells was noted ($p=0.049$). Pre-irradiation 0.05 Gy + PS 10 mg/kg + RT 2 Gy vs. pre-irradiation 0.05 Gy + RT 2 Gy - a decrease in the number of viable RT4 cells was noted ($p<0.00001$).
Rutkov-skienė L. *et al.*, 2011 [10]	Lithuania	C6 rats glioma	hematoporphyrin derivative (HpD) 1 μg/ml mTHPC (temoporfin) 0.1 μg/ml	^{60}Co source AGAT-R1 A dose rate of approximately 1.1 Gy/min. Single focal doses 2-4-6-8 Gy	The radiosensitized treatment of cells with HpD resulted in a significant ($p<0.05$) decline in cell survival as compared with irradiation alone. For C6 treated with mTHPC, the results did not differ between the two groups (with and without the drug).
Benayoun L. *et al.*, 2013 [11]	Israel	U-87MG human glioblastoma	Photofrin II, 1 μg/ml	6 MeV electron beam using Elekta Precise linear accelerator Dose rate of 5 Gy per minute A total dose of either 3 Gy or 10 Gy	A U-87MG tumor cell population enriched with radiation-resistant TICs becomes radio-sensitive, and an inhibition of cell proliferation and an increase in apoptosis are found in the presence of Photofrin II.
Takahashi J. *et al.*, 2013 [12]	Japan	B16-BL6 mouse melanoma	5-ALA 5, 10, 50, 100 μg/ml	X-ray generator KXO-15E 100 kV, 4 mA A total doses were 1, 3, 5 and 10 Gy.	ALA facilitates PpIX accumulation in tumor cells and enhances ROS generation *in vitro*.

(Table 1). Continued.

Authors/ references	Country	Tumor cell culture	PS, dose	RT regimens	Antitumor efficacy
Yamamoto J. *et al*., 2015 [3]	Japan	9L gliosarcoma	5-ALA 100 μg/ml	X-ray irradiator MBR-1520R A rate of 0.65 Gy/min. Single focal dose was 8 Gy or 2 Gy for 4 days.	The authors reported that the results obtained indicate the sensitivity of gliosarcoma 9L to ionizing radiation in combination with the addition of 5-ALA to the nutrient medium with a single exposure ($p<0.05$). The number of viable 9L cells under the same exposure regime did not statistically differ from the control group (without exposure) ($p=0.096$). In the case of multiple irradiation (2 Gy for 4 days = 8 Gy), the radiosensitivity was higher in both cell lines ($p<0.05$).
Matsuyama Y. *et al*., 2022 [2]	Japan	mouse osteosarcoma LM8 human prostate cancer PC-3 human breast cancer MDA-MB-231	Acridine orange (AO) 0.1-1 μg/ml	Tumor cells irradiated with 3 or 5 Gy.	In LM8 cells, at a concentration of 1 μg/ml AO, the 5 Gy dose showed a significant decrease in cell proliferation, compared with 0 Gy ($p=0.001$) and 3 Gy ($p=0.007$). In MDA-MB-231 cells, at a concentration of 1 μg/ml AO, a significant decrease in cell proliferation was observed at radiation doses of 3 Gy ($p=0.003$) and 5 Gy ($p=0.001$) when compared with that in the non-irradiated groups. In PC-3 cells, at an AO concentration of 1 μg/ml, radiation doses of 3 Gy ($p=0.002$) and 5 Gy ($p=0.006$) resulted in a significant decrease in cell proliferation when compared with that in the non-irradiated groups.
Di Pompo, G. *et al*., 2022 [13]	Italy	Human breast carcinoma (MCF7 and MDA-MB-231) Renal carcinoma (Caki-1 and ACHN)	Acridine orange (AO) 1 μg/ml	X-ray occasion (34 kV, 7 s). Cells were then exposed to 1 and 5 Gy of X-ray. An irradiation rate of 1.4 Gy/min.	According to our data, AO-RDT is selectively toxic in carcinoma cells and significantly inhibits tumor-induced osteolysis, both *in vitro* and *in vivo*.

experimental studies *in vitro* and *in vivo* were «Hematoprophyrin» and «Photofrin II» [6, 7].

RADIODYNAMIC THERAPY IN EXPERIMENTAL ONCOLOGY

In the available literature sources, there are only a few publications (by author groups from Germany, Lithuania, Israel and Japan) on the *in vitro* (Table **1**) [2, 3, 8-12] and *in vivo* (Table **2**) [2, 4, 12-15] studies of the radiosensitizing effect of PS («Hematoporphyrin», «Photofrin II», «5-aminolevulinic acid» (5-ALA) and «Acridine orange» (AO).

The data obtained in experiments on cultures of tumor cells and laboratory animals with transplanted tumors indicate a high antitumor efficacy of the RDT with various types of PS. This fact is confirmed by a statistically significant decrease in viable tumor cells with the combined use of RT and PS, as well as a pronounced inhibition of the growth of transplanted

Table 2: Antitumor Efficacy of Radiodynamic Therapy in an *In Vivo* Experiment

Authors/ references	Country	Tumor cell culture	PS, dose	RT regimens	Antitumor efficacy
Schaffer M. *et al.*, 2001 [14]	Germany	subcutaneously transplanted bladder carcinoma RT4 nude mice	Photofrin II, 10 mg/kg	Siemens X-Rays device 50 kVP, 25 mA. A total dose of 5 and 15 Gy	The tumor doubling time (tumor growth) enhanced from 5.9 days – control group, 6.4 days – Photofrin II only, irradiation 5 Gy only – 6.4 days, irradiation 15 Gy only – 8.4 days to 10.9 days in group with the use of irradiation 10 Gy and injection of Photofrin II.
Schaffer M. *et al.*, 2002 [4]	Germany	subcutaneously transplanted Lewis sarcoma Balb/c mice	Photofrin II from 0,5 to 5 mg/kg 5-ALA from 20 to 200 mg/kg	Siemens X-Rays device 50 kVP, 25 mA. Irradiation was carried out once in the single focal dose 3 Gy.	The optimal mode of exposure was the combined use of «Photofrin II» (5 mg /kg) + RT 3 Gy (0.65±0.03 cm^3). This indicator was significantly less than in the rest of the study groups, including a combination of 5-ALA at doses from 20 to 200 mg/kg with RT, «Photofrin II» (0.5 mg/kg) + RT and RT in mono mode (1.15-1.29 cm^3; $p>0.05$)
Takahashi J. *et al.*, 2013 [12]	Japan	B16-BL6 mouse melanoma C57BL/6 J mice	5-ALA 50 mg/kg	X-ray generator KXO-15E 100 kV, 4 mA. A dose rate was 1.007 Gy/min at the sample stage. Tumor were irradiated with 3 Gy daily quaque die × 5 × 2 weeks, for a total dose of 30 Gy.	Tumor suppression significantly improved in animals treated with fractionated doses of radiation (3 Gy × 10; total, 30 Gy) with local administration of 50 mg/kg 5-ALA at 24 h prior to fractional irradiation ($p<0.05$).
Matsuyama Y. *et al.*, 2022 [2]	Japan	mouse osteosarcoma LM8 human prostate cancer PC-3 human breast cancer MDA-MB-231 C3H/HeSlc mice BALB/cSlc-nu/nu mice	Acridine orange (AO) 1 µg/ml	Tumor were irradiated with 5 Gy.	In xenograft mouse model, the AO-RDT also showed a strong cytocidal effect on tumour at the backside in osteosarcoma, breast cancer, and prostate cancer. The changes in tumour volume (mm^3) during 14 days after treatment in xenograft model: LM8: control – 890, AO -780, RT – 120 and AO + RT – 42 mm^3 ($p<0.05$) MDA-MB-231: control – 1060, AO -620, RT – 1010 and AO + RT – 29 mm^3 ($p<0.05$). PC-3: control – 530, AO -200, RT – 45 and AO + RT – 14 mm^3 ($p<0.05$) In all models, there was no significant difference in the number of lung metastases between groups ($p = 0.353$ for LM8, $p = 0.078$ for MDA-231, and $p = 0.166$ for PC-3).

(Table 2). continued

Authors/ references	Country	Tumor cell culture	PS, dose	RT regimens	Antitumor efficacy
Di Pompo, G. *et al*., 2022 [13]	Italy	Human breast carcinoma MDA-MB-231 Balb/cnu/nu mice	Acridine orange (AO) 5 mg/kg	X-ray occasion (34 kV, 7 s). Tumors were exposed with single focal dose of 5 Gy. An irradiation rate of 1.4 Gy/min.	AO-RDT was selectively toxic only for carcinoma cells and effective to impair both tumor expansion in bone and tumor-associated osteolysis.
Yang D.M. *et al*., 2022 [15]	USA	subcutaneous model KP1 small-cell lung cancer C57BL/6 mouse	5-ALA 100 mg/kg	4 Gy in a single fraction was delivered to the tumors using 15MV photons.	RDT (5-ALA + RT) achieved a statistically significant delay in tumor growth by 52.1%, 48.1%, and 57.9% 7 days post-treatment compared to 5-ALA only, RT only, and control group (P<0.001), respectively. There were no significant differences in tumor growth between 5-ALA only and RT only groups. An additional 38.5-40.9% decrease in tumor growth was observed, showing a synergistic effect with RDT (5-ALA + RT).

tumors compared with the control groups, including the group of radiation therapy in mono mode.

RADIODYNAMIC THERAPY IN CLINICAL ONCOLOGY

Various scientific teams are making attempts at clinical testing of the RDT method («Gammadynamic therapy»). The greatest experience in the use of RDT in clinical oncology is represented by Lithuanian scientists from the Vilnius Cancer Center. In a study by L. Bloznelytė *et al*. (2002) included 97 patients with various nosological forms of malignant neoplasms. PS «Hematoporphyrin» was administered intravenously at a dose of 5 mg/kg. 24, 48, and 72 hours after the end of its infusion, the tumor was irradiated with γ-radiation in single focal dose of 2 Gy (3 fractions, total focal dose 6-9 Gy). The authors report about minimal risk of serious adverse reactions. The frequency of complete tumor regressions was noted in 40 observations; partial regression more than 75% - 37, partial regression more than 50% - 42 and partial regression more than 20% - 32. No effect was registered in 22. The frequency of complete regressions in patients with disseminated melanoma was 22.2% (in 18 of 81 observations), with osteogenic sarcoma - 71.4% (in 5 out of 7), with lymphosarcoma - 60% (in 5 out of 7), etc. [16].

German scientists led by M. Schaffer *et al*. (2002) presented the results of treatment of 2 patients with unresectable recurrent forms of bladder cancer. PS «Photofrin II» was administered intravenously at a dose of 1 mg/kg. Tumor irradiation was started 24 hours after the end of a single PS infusion, the total focal dose was 44.8+14 Gy. The authors reported no serious adverse reactions, and the technique used made it possible to reduce tumor volume by 35% and 40%, respectively. After completion of the course of RDT and RT, the patient underwent surgery [17].

In another study, M. Shaffer *et al*. (2006) presented the experience of using RDT in 7 patients with unresectable forms of malignant tumors (bladder, n=4), pelvic sarcomas, n=2), cervix cancer, FIGO IV, n=1). PS «Photofrin II» was administered intravenously at a dose of 1 mg/kg. Tumor irradiation was started 24 hours after the end of a single PS infusion, the total focal dose was 44.4-50.4 Gy. All patients had contraindications to chemotherapy courses. There were no serious adverse reactions after treatment (skin phototoxicity, CTCAE grade 1, n=3), diarrhea (CTCAE grade 1, n=2; CTCAE grade 2, n=3), cystitis (CTCAE grade 1, n=4), nausea (grade 1 CTCAE, n=3; grade 2 CTCAE, n=1), vomiting (grade 1 CTCAE, n=2; grade 2 CTCAE, n=1).The median follow-up was 12.9 months (4-32 months) Patients with cervical cancer (FIGO IV) and pelvic sarcoma had long-term remissions without signs of progression (27 and 28 months, respectively). In 1 patient with pelvic sarcoma, a 40% reduction in tumor volume was noted, which allowed for special treatment (chemotherapy + hyperthermia). In 2 out of 4

patients with bladder cancer, a reduction in tumor volume by 35-40% and 45%, respectively, was noted, which made it possible to perform surgery. The follow-up period for these patients ranged from 4 to 12 months. However, 3 out of 4 died from the progression of the tumor process (distant metastases) [18].

M. Schaffer *et al*. (2006) studied the possibility of clinical use of PS «Photofrin II» as a RS in 3 patients with astrocytomas (WHO, grade III). Irradiation was performed with total focal doses of 30-60 Gy and started 24 hours after a single intravenous administration of PS at a dose of 1 mg/kg. The observation period varied from 5 to 15 months. No serious adverse reactions were noted. The patient with a recurrent form of the disease died due to the progression of the tumor process after 5 months. after the treatment. In a patient with a primary form - within 14 months follow-up showed no signs of progression, and the second one showed complete regression of the tumor [18].

In another study, P. Schaffer *et al*. (2019) reported on the possibility of treating a patient with unresectable carcinoma of the cervix (FIGO IIIb) with the use of RDT. PS «Photofrin II» was administered intravenously at a dose of 1 mg/kg, and irradiation began 24 hours later at single focal doses of 1.8-2 Gy 5 times a week until total focal dose of 50.4+14 Gy. Local recurrence of the disease was detected 30 months after the end of the course of treatment and successfully operated (hysterectomy). The patient is alive without signs of disease progression (more than 15 years) [19].

Clinical trial «A Phase I Dose Finding Study Of Low-dose Radiation With Sensitization Using 5-aminolevulinic Acid In Advanced Malignancies» started at the Fox Chase Cancer Center (USA) in May 2020. The study is planned to include 130 patients with different nosological forms of tumors. This is a phase 1, open label, dose-escalation, safety, pharmacokinetic, and pharmacodynamic study to determine the maximum tolerated doses or recommended phase 2 doses of both ALA and RT. Patients enrolled in this study will receive 3 doses of ALA and fractions of RT during the course of one 21 day cycle. Only one cycle per patient is allowed. Patients are followed through day 56 for adverse event and efficacy measures [20].

In October 2022, a clinical trial «Phase I/II Dose Escalation Trial of Radiodynamic Therapy (RDT) With 5-Aminolevulinic Acid in Patients With First Recurrence of Glioblastoma» started under the guidance of a professor Stummer W. (University Hospital Münster, Germany). The study is planned to include 34 patients with a verified diagnosis. The investigational drug 5-ALA (Gliolan®) is an approved drug for the surgical removal of malignant glioma (WHO grade III and IV). In this trial, the drug is being tested outside of its actual approval as a radiosensitizer in combination with conventional RT for first-time recurrence (relapse) of malignant glioma. The investigational drug 5-ALA is being used for the first time in a multiple dose escalation regimen in combination with RT following surgical removal of a recurrent malignant glioma in humans. The planned clinical trial will first and foremost investigate how well repeated administration of the investigational drug 5-ALA is tolerated in combination with RT. At the same time, the design of the trial serves to optimize this novel therapeutic procedure with regard to the frequency of administration of the investigational drug 5-ALA in combination with RT for future clinical trials [21].

Several pilot projects have begun testing the RDT method in patients with various malignant neoplasms, including inoperable ones. The preliminary data obtained show good tolerability of the method (no serious adverse reactions), satisfactory antitumor efficacy (an increase in the frequency of objective responses and an increase in the % reduction in tumor volume, which made it possible to transfer them to a resectable state). However, the paucity of treated patients, the lack of results of randomized trials and the need for their implementation in order to optimize the modes of exposure to ionizing radiation and determine the effectiveness of RDT in a comparative aspect with RT in monomode, does not allow us to draw final conclusions about the prospects for the application of this scientific area in clinical practice.

CONCLUSION

PDT is a light-based method that uses photo-reactive molecules, such as different types of PS, to destroy malignant tumors. As some authors testify, PS was shown to act as a radio-reactive molecule by enhancing generation of reactive oxygen species upon X-ray irradiation. The method of treatment, which is based on the combined use of PS and ionizing radiation, is called «Radiodynamic therapy» (RDT). The advantage of RDT over PDT is the X-ray's penetrability through tissues, which will find many applications for treatment of deep malignant tumors. The authors of a number of research centers in Japan, Germany, Israel and Lithuania presented the

experience of using RDT in experiments on tumor cell lines. A clinical approbation of the method has been started in patients with unresectable forms of bladder and cervical cancer, with gliomas and other forms of malignant tumors. The data obtained in experiments and during clinical testing on small numbers of patients indicate the relevance and promise of further research in the area of RDT.

FUNDING

None.

ACKNOWLEDGEMENTS

The authors declare no conflict of interest.

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Received on 11-11-2022 Accepted on 15-12-2022 Published on 28-12-2022

https://doi.org/10.30683/1927-7229.2022.11.11