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Research Article

Nanosense: Nonsurgical treatment of superficial cancer by (PLAN)

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Abstract

Under current development is Nanosense**,** a medication designed for the nonsurgical treatment of superficial cancer via pulsed laser ablation of nanoparticles (PLAN). Nanosens is a stable dispersion of phthalocyanine zinc nanoparticles in a physiological solution. The technology for obtaining stable dispersions of zinc phthalocyanine ensures a shelf life of over two years. This article presents preliminary data from preclinical studies of the Nanosens formulation. Results were obtained on the effectiveness, pharmacokinetics, and biodistribution of the Nanosens drug in mice, as well as toxicity and allergy studies. When tested at therapeutic doses (1 TD = 7 mg/kg) ranging from 1 to 10 TD for acute toxicity and from 1 to 30 TD for chronic toxicity, no signs of intoxication leading to death were observed in animals. However, at the maximum dose, individual organs and tissues exhibited a blue coloration.

Keywords

Nanosense, nonsurgical, treatment, PLAN, phthalocyanine, photodynamic, tumor, nanotechnology, toxicity, microexplosive, ablation

Introduction

Today, some of the concerns in public health revolve around resistance and cancer, leading to the loss of more than 15 million lives annually. This highlights a decline in the effectiveness of antibiotics and chemotherapy treatments. One proposed solution is the application of nanotechnology.

One of the most significant achievements of recent years is the study of methods for obtaining the properties of nanoparticles, quantum dots, and other nano-sized objects. The number of publications on this topic is rapidly increasing, with the first examples of commercial applications of nanomaterials emerging.

Since this field of science began to be thoroughly explored relatively recently, there is still no clear classification of nanoparticles. However, three distinct groups of nanoparticles can be identified: metal nanoparticles, nanoparticles of inorganic compounds, and organic nanoparticles. The first two groups have been studied in sufficient detail, with extensive literature on their synthesis, optical and semiconductor properties, and research methods. In contrast, organic nanoparticles are much less studied, with only a few articles focusing on the synthesis and investigation of nanoparticles of phthalocyanine dyes and some other organic compounds.

Based on literature analysis, the question of the sizes of organic nanoparticles and methods of their measurement, as well as the influence of the size parameter on the manifestation of photo-physical effects, remains insufficiently explored in this area of knowledge. Research methods in electron microscopy and small-angle X-ray scattering are not well suited here: firstly, organic nanoparticles are largely transparent to electrons and X-rays, and secondly, strong impacts, such as electron beam exposure, contribute to their destruction. It becomes evident that nanoparticles are better studied in the matrix in which they were synthesized, and non-destructive methods of control should be used for their investigation (Gulbinas et al. 1994; Wang et al. 1999; Akimov et al. 2003; Denisyuk and Kamanina 2004).

The sizes of crystalline nanoparticles appear to stay constant without any changes over time. For instance, the size of Mg phthalocyanine nanoparticles is 2 nm in the β form. 2.5 nm in the X form, aligning with the sizes of cells within the crystalline lattice of their respective polymorphic forms. It is proposed that each nanocrystal consists of two cells from the crystalline lattice, ensuring its stability. On the other hand, amorphous modification nanoparticles are less stable; their sizes tend to increase from 12 to 22 nm during storage, eventually leading to colloid precipitation (Butyanov et al. 2005).

A Russian scientist (Kogan et al. 2004; Pankratov et al. 2014) has discovered that photoactive aluminum phthalocyanine nanoparticles, zinc phthalocyanine, and metal-free phthalocyanine, under the influence of pulsed laser radiation, can form molecular forms that act as photosensitizers. Phthalocyanines are organic dyes that are inert, non-toxic, and insoluble in organic solvents and water. It has been found that phthalocyanine nanoparticles can be used as effective "pro-photosensitizers" for the treatment of malignant tumors using photodynamic therapy. Activation of a photoactive nanoparticle into a photoactive molecular photosensitizer occurs locally within the tumor nods by irradiating with powerful laser pulses. During this process, the nanoparticle explodes, exhibiting photosensitizer properties. Such "generated" photosensitizer directly within the tumor can be used to conduct conventional photodynamic therapy.

The main drawback of conventional photosensitizers is their cutaneous phototoxicity, manifested by increased photosensitivity of the skin and the need for protection from sunlight. In this case, even with repeated administration of AIPc, ZnPc, and H2Pc nanoparticles, there was no accumulation of their photoactive form in the skin, which could contribute to the development of skin phototoxicity.

As a result of the conducted research, effective protocols for photodynamic therapy using a medical preparation (Nanosense) containing zinc photalocyanine nanoparticles in the form of an aqueous suspension have been identified.

The pharmaceutical preparation Nanosense is a bright blue liquid—a stabilized nanodispersion of zinc phthalocyanine (see Fig. 1) in physiological saline. The content of the active substance in the preparation is 2 mg/mL. The average particle size of zinc phthalocyanine is 150–250 nm. The shelf life of the preparation is at least two years.

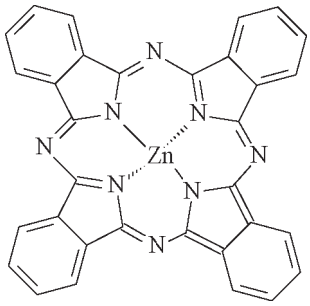

Figure 1. Zinc Phthalocyanine.

Nanosense is the first pharmaceutical preparation designed for the treatment of skin cancer using the method of pulse laser ablation nanoparticles (PLAN).

Materials and methods

The study of the antitumor effectiveness of the Nanosens was carried out using the PLAN method against transplantable tumors of mice of various histogenesis.

Equipment used in the study: as a source of powerful pulsed laser radiation, we used a pulsed ruby laser (λ=694 nm; pulse duration 40 ms), operating in the modulation mode (Pockels cell) of the resonator Q factor (irradiation parameters are presented in the designs of the corresponding studies). Manufacturer: FSUE "SSC "NIOPIK". The PLAN method was developed jointly by scientists from FSUE "GNC "NIOPIK" FSBI "MNIOI named after P.A. Herzen" (Kogan et al. 2004, 2006, 2008, 2010, 2011a, 2011b; Andreeva et al. 2012; Pankratov et al. 2014). It is protected by three patents (RF Patent 2008; RF Patent 2010; Patent RU 2017). The technology for producing the Nanosense preparation was developed at the FSUE "GNC "NIOPIK".

The methodology for studying the antitumor effectiveness was carried out depending on doses of the drug, time interval between drug administration and pulsing irradiation, parameters of pulsed laser radiation, energy density per pulse, and number of pulses. The initial dose of Nanosens was 15 mg/kg.

Optimal regimen for the PLAN procedure with the drug Nanosens: intravenous administration of the drug Nanosens (15 mg/kg or 7 mg/kg), 2–5 min pulsed irradiation (energy density per pulse: 0.6 J/cm2; number of pulses: 100 or 50).

Research was conducted on mice with the following implanted tumors: B16 melanoma, Lewis lung carcinoma LLC, S-37 sarcoma, C-26 carcinoma, Ehrlich tumor, cervical cancer RShM5, and the solid form of leukemia P-388. For experiments, tumors were inoculated into mice under the skin on the outer surface of the thigh in different amounts of tumor tissue per animal. The day of tumor inoculation was considered day zero of its growth. Treatment of mice with P-388, S-37, OE, S-26, and LLC was carried out on days 6–7 after inoculation of tumor material, and mice with CC on days 10–12.

After the tumors had taken root, mice were injected intravenously with the drug Nanosens, and after 2–5

minutes, nanoparticles of zinc phthalocyanine entered the bloodstream and accumulated in the tumors. The tumor was irradiated with a 7 ns pulsed laser with a wavelength of 664 nm, about 100 MW in pulse, while the nanoparticles were heated to temperatures above 400 degrees Celsius and exploded. Fragments of nanoparticles damaged tissues and the circulatory system of the tumor.

When exposed to a pulsed laser on nanoparticles of zinc phthalocyanine in a tumor, in addition to fragments of nanoparticles, a molecular form of zinc phthalocyanine is also formed, which has photosensitizer properties and is suitable for classical photodynamic therapy. In this case, we can talk about targeted delivery of the photosensitizer exactly to the tumor. In this way, it is possible to further enhance the effect of the drug on the tumor, which causes its degradation and death.

Study of the "acute" toxicity of the drug Nanosens. The doses and route of administration of the Nanosens drug to study its "acute" toxicity were chosen based on a single therapeutic dose (TD) of the drug. When studying the "acute" toxicity (tolerability) of Nanosens with the PLAN procedure in mice, the following dose levels were studied: TD; 2.5TD; 5TD; 7.5TD; 10TD. The drug was administered to mice (males and females) once (or in small doses with an interval between injections of no more than 15 min) intravenously in the doses indicated above. Control animals were injected with an isotonic (0.9%) sodium chloride solution. Pulsed irradiation of the hind limb and thigh was performed. 2–5 min after drug administration.

When choosing doses of the drug to study its "chronic" toxicity in rats, we proceeded from the equitherapeutic dose for rats (ETDr), which was calculated on the basis of the maximum therapeutic dose for mice equal to 15 mg/kg, considering the coefficient of interspecies according to the Freireich method (Freireich et al. 1966) and amounted to 7 mg/kg. When studying the "chronic" toxicity of the Nanosens drug in rats, the following dose levels were studied: ETDr; 10ETDr; 30ETDr. Control animals were injected with an isotonic (0.9%) sodium chloride solution. Pulsed irradiation of the hind limb and thigh was performed. 2–5 min after drug administration. Nanosens was administered to rats once a day for 14 days intravenously at the doses indicated above. Control animals were injected with an isotonic (0.9%) sodium chloride solution.

Immunotoxicity study: In the experiments, we used conventional animals to study the effect of the studied drug on delayed-type hypersensitivity (DTH) in linear mice as well as on the humoral immune response in linear mice (hemagglutination reaction). The total number of animals in the study was 60 mice. In the study, we used animals of the same body weight as possible.

Studying pharmacokinetics was carried out using the Spectrometer Ocean Optics (the device was used to measure and record electronic absorption spectra of blood plasma samples after administration of the Nanosens drug) and the Autosizer 2C device (the device was used to measure the size of nanoparticles in blood plasma samples after administration of the Nanosens drug).

While the biodistribution study was carried out using a high-energy pulse laser, a pulsed laser was used to obtain the molecular form of ZnPc from nanoparticles (Nanogsens preparation) through high-energy pulsed irradiation. The study used a pulsed dye laser (emission wavelength 670 nm, pulse energy 45 mJ, pulse duration 8 ns) pumped by the second harmonic of the Nd:Yag laser. In addition, an installation for recording fluorescence spectra was installed (an Ocean Optics optical fiber spectrometer was used to record the fluorescence spectra of the molecular form of ZnPc.).

List of abbreviations

PLAN	pulsed laser ablation of nanoparticles;
TD	therapeutic dose;
ZnPc	photosensitizers zinc phthalocyanine;
H2Pc	metal-free phthalocyanin;
LLC	Lewis lung carcinoma;
LD50	lethal dose.

Results of preclinical studies of the drug Nanosens

Tests for effectiveness, chronic toxicity, acute toxicity, and immunotoxicity were carried out. The range of therapeutic doses of the Nanosens drug and the optimal parameters of pulsed laser radiation were determined.

In all cases, after a single PLAN procedure, we observed inhibition of tumor growth, an increase in life expectancy in the case of S-37 sarcoma and Lewis LLC lung carcinoma, and even a complete cure for some animals. Effect leading to inhibition of the growth of the number of transplantable tumors in mice by 100%–50%; an increase in the average life expectancy of animals by 25%–77%; as well as complete cure of the tumor in 8%–25% of mice.

Thus, by summarizing the data obtained during the study of the antitumor effectiveness of the Nanosens using the PLAN method in mice with transplantable tumors of various histogenesis (C-26 carcinoma, Lewis lung carcinoma, Ehrlich carcinoma, RSM5 cervical cancer, P-388 lymphocytic leukemia, S sarcoma-37, and melanoma B-16), it was established that the treatment procedure in the experiment is a highly effective method of antitumor therapy.

It has been established that C-26 carcinoma, S-37 sarcoma, and Lewis lung carcinoma are the most sensitive tumors to this type of treatment; cervical cancer RSM-5, Ehrlich carcinoma, and melanoma B-16 have average sensitivity; and the solid form of lymphocytic leukemia P-388 turned out to be a tumor resistant to treatment with Nanosens using the PLAN method.

Data on the toxicity (Tables 1, 2) of the drug in therapeutic doses were obtained. At the preliminary stage of research, the limit of the semi-lethal dose LD50 of zinc phthalocyanine when administered orally was determined (LD50>10g/kg). It was not possible to establish it more precisely since no deaths of animals were observed. As expected, when testing the drug at therapeutic doses (1 TD=7mg/

Table 1. Death of mice from toxicity after the PLAN procedure with Nanosens, depending on the dose of the drug.*

Group No.	Test drug or control substance	Dose drug, mg/kg	Total number of animals	Animal death from toxicity		
				total / died	%	time of death, days
ILAN PROCEDURE:						
IV administration of the drug Nanosens, 2–5 min → pulsed irradiation laser pulse irradiation parameters:						
- energy density per pulse: 0.6 J/cm2;						
- number of pulses: 50						
Males						
1	**Nanosense**	15	6	6/0	0	-
2	**Nanosense**	37.5	6	6/0	0	-
3	**Nanosense**	75	6	6/0	0	-
4	0.9% NaCl solution	25 ml/kg	6	6/0	0	-
Females						
1	**Nanosense**	15	6	6/0	0	-
2	**Nanosense**	37.5	6	6/0	0	-
3	**Nanosense**	75	6	6/0	0	-
6	0.9% NaCl solution	25 ml/kg	6	6/0	0	-

* - in groups 3 and 4, Nanosens and 0.9% sodium chloride solution were administered fractionally: 2 times with an interval of 15 minutes (due to the large volume of injected liquid).

Table 2. Death of animals from toxicity and external signs of intoxication in rats after 14-fold intravenous administration of the drug Nanosens.

Drug dose, mg/kg		Death from toxicity, %	Dose characteristics. External signs of intoxication
one-time	total		
0.5	**7.0**	0 (n = 20)	$ETDk_r$ of intoxication.
5.0	**70.0**	0 (n = 20)	$10ETD_r$. There were no external signs of intoxication. observed coloration of animal skin in a bluish color
15.0	**210.0**	0 (n = 20)	$30ETD_r$. There were no external signs of intoxication. observed coloration of animal skin in a bluish color
Control substance (0.9% sodium chloride solution)			
8 ml/kg	112 ml/kg	0 (n = 20)	There were no external signs of intoxication.

Non-inbred rats, males. ETDr – calculated equitherapeutic dose for a rat.

kg) in the range of 1 to 10 TD for acute and in the range of 1 to 30 TD for chronic toxicity, no death signs of intoxication were observed in animals, although at the maximum dose, individual organs and tissues acquired a blue color.

The immunochemical study shows the results of assessing the effect of the drug Nanosens on the severity of IHR6, which are presented in Tables 3, 4.

According to the data obtained in a model of immune swelling of the paw in mice when stimulated with sheep erythrocytes, it was found that under the influence

Table 3. Effect of the study drug on the amount of paw edema in mice.

Dose, mg	Weight of the control foot, mg (M ± m)		Weight of experimental paw, mg (M ± m)		Reaction index, % (M ± m)	
Control	124.0	8.9	224.0	17.0	82.1	9.8
Investigational drug "Nanosense "						
6.7 mg/kg	128.0	11.0	238.0	14.5	86.0	7.7
67.0 mg/kg	132.0	11.0	212.0	19.5	**60.5***	**5.6**

Notes: * - statistically significant difference (calculations were made using the Student's t-test at $p \leq 0.05$).

Table 4. Effect of the study drug on the titer of hemagglutinins in the blood serum of mice.

Dose, mg	Hemagglutinin titer, M±m
Control	84.0 ±29.5
Investigational drug "Nanosense "	
6.7 mg/kg	68.0 ±19.3
67.0 mg/kg	**60.0 ±21.0***

Notes: * - statistically significant difference (calculations were made using the Student's t-test at $p \leq 0.05$).

of a 14-day course of intravenous administration of the study drug at a dose of 10 T (10 times higher than the therapeutic dose for a mouse), the reaction index was significantly lower by 20% than the control indicator, that is, the effect of drugs at a dose of 67.0 mg/kg led to inhibition of the development of immune inflammation.

The results of a study assessing the effect of the Nanosens drug on the humoral immune response of mice are presented in Table 4.

From the data present in Table 4, it can be seen that the determination of the drug Nanosens in experimental doses led to a change in the serum titer, while intravenous administration of the drug at a dose of 67.0 mg/kg caused a significant decrease in their titer of hemagglutinins compared to control values.

When studying biodistribution (Table. 5), it was found that after a single intravenous administration of the drug Nanosens at a therapeutic dose of 7 mg/kg, nanoparticles predominantly accumulate in the liver, lungs, spleen, and kidneys and are then slowly excreted from these organs (for more than 60 days). The peak accumulation of zinc phthalocyanine nanoparticles in tumor tissue was recorded 24 hours after intravenous administration of the drug.

Table 5. Fluorescence intensity of the molecular form of ZnPc in the internal organs and tissues of mice after a single-dose intravenous administration of the drug Nanosens, followed by irradiation of the target organ or tissue with powerful laser pulses.

Organ/ tissue	Fluorescence intensity of the molecular form of ZnPc (I fl ZnPc m), a.u. period after administration of the drug Nanosens									
	5 minutes	1 hour	4 hours	24 hours	3 days	7 days	14 days	21 days	30 days	60 days
Heart	7400±3175	5000±1732	4667±1155	5333±289	6167±2754	3333±1528	3333±577	2667±577	1667±289	1267±58
Lungs	26000±16523	23000±4583	35000±13229	39000±7937	21000±5196	26667±12858	12000±7810	15000±7550	14333±1520	4000±500
Liver	36667±4933	33667±7234	36000±6000	41000±1732	26667±13317	20000±5292	22333±7234	22333±2517	14333±1528	14167±2363
Kidneys	14333±2517	17000±1732	14167±4646	10333±3215	12667±3215	11647±577	10362±1528	10333±2082	7667±2309	6100±794
Spleen	16333±6658	26000±4000	19000±3464	12000±4359	8333±577	15333±6429	16667±3512	12000±1000	6333±3055	4933±814
Intestine	8000±1000	15000±5196	10000±4583	16833±4368	19000±3464	7333±2309	9000±1000	8667±7234	4333±3512	1850±1213
Leather	3833±2843	10000±4583	6833±1893	4667±4041	4333±2082	5667±1528	7333±1155	8667±1528	4167±1756	4000±1000
Muscle	5000±1000	6833±6212	3333±577	3000±500	2833±764	2667±1155	2167±289	2000±866	1833±1443	800±100
Tumor	5010±2656	8152±2610	7864±588	14677±2567	9000±1000	5638±1344	2005±1482	n/a	n/a	n/a

Hybrid mice, female, intact, and with S-37 sarcoma. Nanosens was administered intravenously once at a dose of 7 mg/kg. n/i – the study was not carried out due to the development of necrosis in the tumor node by the 15th day of its growth.

Table 6 presents the pharmacokinetics results. It can be seen that the particle sizes practically do not change during their circulation in the bloodstream for 24 hours.

Table 6. Size distribution of ZnPc nanoparticles in mouse blood plasma samples obtained at various time intervals after intravenous administration of the Nanosens drug.

Time after administration of Nanosens	Particle sizes of zinc phthalocyanine, nm			
	D naive.	D Middle-Ar.	D min.	D max.
1 min.	160±11	190±5	100±2	480±7
5 minutes.	150±5	210±10	100±6	540±5
15 minutes.	140±10	180±10	90±5	420±10
30 min.	160±10	200±10	100±5	500±5
1 hour	160±7	210±7	100±2	100±7
2 hours	140±5	200±5	100±5	490±5
4 hours	150±10	220±10	110±5	520±5
6 o'clock	150±10	230±10	110±5	590±5
24 hours	130±6	230±9	90±5	550±3
Control. **Nanosense** drug	160±5	200±10	110±5	470±5

Nanosens was administered to mice once intravenously at a dose of 15 mg/kg. D naive. – most probable, D Middle Ar. mean arithmetic, D min. – minimum, D max. – maximum particle size.

After intravenous administration of Nanosens at a therapeutic dose of 15 mg/kg, nanoparticles are completely eliminated from the blood of animals within 24 hours. The experimentally determined half-life of nanoparticles in the blood was 1 hour. After intravenous administration of Nanosens, during the entire time of its circulation in the blood (24 hours), there is no significant change in the size of ZnPc nanoparticles.

It was found that Nanosens does not affect blood clotting and does not have hemolytic activity. It was also found that at concentrations of 2 mg/mL and lower, the drug does not have an irritating effect when administered intravenously. The PLAN procedure with the drug Nanosens, which was used in doses ranging from 15 mg/kg to 75 mg/kg, was satisfactorily tolerated by all animals. There was no death of animals from toxicity. No pronounced external signs of intoxication were observed. During a postmortem examination of animals euthanized 90 days after administration of the drug, no pathological changes were detected in the internal organs and tissues of the animals.

The study did not reveal any allergic effects of Nanosens detected in the "Conjunctival test" in pre-sensitized mice at doses of 8 mg/kg and 80 mg/kg.

Conclusions

The essence of the PLAN method is that powerful-pulsed laser radiation is directed at the nanoparticles of the drug introduced into the tumor. As a result, the nanoparticles are locally heated, leading to their microexplosive ablation, which damages the tumor tissue as well as its feeding capillaries. This leads to the suppression of the tumor, halting and inhibiting its growth, and, in some cases, regression and scarring. Thus, PLAN is a non-surgical method for treating superficial tumors. Nanosense can also be used for treatment using the PLAN method combined with photodynamic therapy. In this case, the treatments are administered sequentially.

A new technology has been developed for producing drugs; a photosensor for intravenous administration can be used in the treatment of varicose oncological disease of the skin and mucous membranes using one of the variants of the photodynamic therapy methods, the method of pulse laser ablation of nanoparticles (PLANB). The drug is administered intravenously, and nanoparticles of the drug enter the capillary network of the tumor, where they explode when irradiated with a powerful pulsed laser.

The tumor is irradiated with a powerful pulsed laser with a wavelength in the absorption region of zinc phthalocyanine nanoparticles. Nanoparticles that absorb light at the laser radiation length quickly heat up and explode (nanoparticle ablation), thereby destroying tumor tissues and their capillary systems, which leads to tumor suppression, degradation, and, in some cases, death after a single application.

Declarations

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee in the Faculty of Medicine and Laboratory for the synthesis of pharmaceutical substances and standard samples of the scientific research and development center "Pharmacia," RUDN, named after. P. Lumumba. The study was conducted in accordance with the ethical standards in the Helsinki Declaration. Informed written consent and questionnaires were obtained from all participants enrolled in the study.

Consent for publication

All authors approve of the publication of this paper. Written consent to publish this information was obtained from all study participants.

Availability of data and materials

The datasets analyzed in the current study are not publicly accessible; the study data were obtained from the original findings of the research of the corresponding author.

Competing interests

The authors declare that there are no conflicts of interest.

Authors' contributions

K. A. V. took part in designing the study and also conducted the experiment, including synthesis and physicochemical analysis. M.B.Z.A. took part in designing the study, reviewing, and proofreading the article. H.M.H.A. and Z.A.A.A. took part in designing the study. They also assisted with the data analysis and wrote the article. O. S. A. also took part in designing the study, reviewing, and proofreading the article.

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