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Targeted delivery of domestic anticancer drugs from the group of aziridine triazines (literature review)

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ABSTRACT

Currently, the targeted delivery of anticancer drugs can significantly increase the effectiveness of therapy, reduce the side effects of systemic chemotherapy, and improve the quality of patients with cancer. This review aimed to summarize data about the domestic antitumor drug 2,4-bis(1-aziridinyl)-6-(2,2-dimethyl-5-hydroxymethyl-1,3-dioxan-5-yl) amino-1,3,5-thriazine (dioxadet), its nanoforms, possibilities of its use in the clinic, and main antitumor nanodrugs clinically introduced in recent years. Library databases (eLibrary, PubMed, CyberLeninka, ResearchGate, Springer, Wiley Online Library, and Elsevier) were searched for relevant information. The literature review summarizes data on the preclinical trials of dioxadet and provides information on its nanoforms, such as nanogels, nanodiamonds, silica particles, and copolymers with lactic and caproic acids. New drug nanoforms open up opportunities to reduce drug side effects and systemic toxicity, maintain optimal therapeutic concentrations, increase the drug circulation time in the blood, and control its release. The possibility of using chemopreparation cytotoxic doses is the main advantage of new nanodrugs. To date, approximately 20 antitumor nanodrugs have been introduced in clinical practice, and some nanodrugs are undergoing preclinical trials or are in various phases of clinical trials. Thus, the development of a new effective nanoform, i.e., dioxadet, makes it possible to ensure targeted drug delivery in higher cytotoxic doses to target cells, increase selective action, and reduce cytostatic toxicity to normal cells.

Keywords: aziridinylthriazine (nanogel, nanodiamonds, copolymers); anticancer nanodrugs.

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Адресная доставка отечественного противоопухолевого препарата из группы азиридинтриазинов (обзор литературы)

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АННОТАЦИЯ

В настоящее время адресная доставка противоопухолевых лекарственных препаратов позволяет значительно увеличить эффективность терапии, уменьшить побочные эффекты системной химиотерапии и повысить качество лечения онкологических больных. Цель исследования — обобщение информации об отечественном противоопухолевом препарате 2,4-бис(1-азиридинил)-6-(2,2-диметил-5-оксиметил-1,3-диоксан-5-ил)амино-1,3,5-триазин (диоксадэт) на сегодняшний день, его наноформах, возможностях применения в клинике и основных противоопухолевых нанопрепаратах, внедренных в клиническую практику за последние годы в мире. Исследование проводилось с использованием поисково-информационных (eLibrary, PubMed, CyberLeninka, ResearchGate, Springer, Wiley Online Library, Elsevier) и библиотечных баз данных. В обзоре литературы обобщены данные по доклиническим исследованиям диоксадэта и приведена информация о разработанных его наноформах, таких как наногели, наноалмазы, наночастицы кремнезема, сополимеры с молочной и капроновой кислотами. Новые наноформы препарата открывают возможности для уменьшения его побочных эффектов и системной токсичности, а также поддержанию оптимальной терапевтической концентрации, увеличению времени циркуляции лекарственного вещества в крови и контролю его высвобождения. Возможность применения цитотоксических доз химиопрепарата является основным неоспоримым достоинством новой лекарственной наноформы. На сегодняшний день внедрены в клиническую практику около 20 противоопухолевых нанопрепаратов, и ряд нанопрепаратов проходят доклинические исследования и различные фазы клинических испытаний. Таким образом, разработка новых эффективных лекарственных наноформ диоксадэта позволяет обеспечить таргетную доставку лекарственного вещества в более высоких цитотоксических дозах к клетке-мишени, увеличить селективность действия, уменьшить токсичность цитостатика в отношении нормальных клеток.

Ключевые слова: азиридинтриазины; наногели; наноалмазы; сополимеры; противоопухолевые нанопрепараты.

Как цитировать

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INTRODUCTION

Despite the intensive advancements of biotherapy, chemotherapy remains one of the main methods of treating cancer patients. Currently, >100 antitumor medicinal substances have been developed [1]. In addition, new drugs are introduced into clinical practice every year, and various therapeutic regimens are tested, which expands the therapeutic possibilities and improves treatment results.

However, the pronounced side effects of systemic chemotherapy significantly limit its potential and significantly worsen the quality of life of patients. The current level of understanding of cancer biology and technical capabilities can significantly increase the therapeutic efficacy and improve the treatment quality of cancer patients. The demand for technologies that detect micrometastases and targeted antitumor drug delivery directly into tumor cells is high. Accordingly, multifunctional carriers should be created for diagnostic and therapeutic purposes. A nanoform (targeted drug delivery system) was developed using nanoparticles with an optimal size of 1–100 nm. Nanoparticles with sizes ranging from 10 to 100 nm are significantly accumulated mainly in tumor tissues due to the delayed effect associated with tumor growth [2, 3]. Nanoparticles carrying targeted molecules to specific tumor markers can directly bind to tumor cells and penetrate inside. Several possible nanoparticle modifications make it possible to increase their circulation time and control the release of therapeutic agents, which together helps reduce damage to healthy tissues, reduces the risk of multidrug resistance, and increases the overall therapeutic efficacy.

Nanoform antitumor drugs targets and can prolong the their effects, protect from premature biodegradation, increase substance bioavailability with suboptimal transport properties, overcome biological barriers including the blood–brain barrier and gastrointestinal tract walls, direct drug transport (tissue- and/or target-specific delivery), control the drug release (reverse response, local or remote activation), maintain the optimal therapeutic concentration of the drug, reduce side effects and systemic toxicity, control the drug interaction with specific biological targets, and determine treatment results at the cellular level.

In the 1990s of the twentieth century, the Research Institute of Oncology named after N.N. Petrov continued the study of a domestic antitumor substance synthesized at the Institute from the group of alkylating compounds of ethylenimines-2,4-bis(1-aziridinyl)-6-(2,2-dimethyl5-hydroxymethyl1,3-dioxane5-yl)amino1,3,5-triazine. The drug has undergone preclinical and clinical trials and has been approved for medical use under the name dioxadet* in the form of a sterile powder in vials for parenteral administration [4, 5].

This literature review provides basic information regarding the domestic antitumor drug dioxadet to date, its nanoforms have already been created, possibilities of use in the clinic, and other major antitumor nanopreparations introduced into clinical practice in recent years. eLibrary, PubMed, CyberLeninka, ResearchGate, Springer, Wiley Online Library, and Elsevier; and library databases; and the State Register of Medicines were searched.

Analysis of the arsenal of cytotoxic drugs revealed that alkylating agents are included in chemotherapeutic regimens for malignant solid tumors and hemoblastoses. Most domestic and foreign studies consider them to be the most promising group of chemotherapeutic drugs [6–8]. Among alkylating agents, platinum preparations, the basis of standard combined tumor treatment regimens, and heterocyclic compounds, are the most widespread.

Drugs substituted 1,3,5-triazines are promising heterocyclic compounds used in modern medical chemistry in the development of active pharmaceutical substances of medicines for the treatment of cancer diseases [9, 10].

Developed and studied at the Federal State Budgetary Institution Research Institute of Oncology named after N.N. Petrov of the Ministry of Health of the Russian Federation, dioxadet, a derivative of ethylene aminotriazines, has unique physicochemical properties, water and fat solubility, allowing it to be administered in fatty (including radiopaque media during chemoembolization of vessels in the liver, kidneys, and other organs based on its inherent pronounced contact antitumor effect in malignant neoplasms of various localizations) and aqueous solutions — in case of tumor effusions into serous cavities [11]. Preclinical comparative studies in the scientific laboratory of cancer chemoprevention and oncopharmacology of the Federal State Budgetary Institution Research Institute of Oncology named after N.N. Petrov of the Ministry of Health of the Russian Federation reported a pronounced contact antitumor effect of dioxadet and the absence of adhesions during intraperitoneal administration [12].

Preclinical studies established the pronounced antitumor activity of the drug on a wide range of transplantable tumors in laboratory animals, such as lymphoid leukemia L1210 (L1210 leukemia), lymphosarcoma LIO1, lymphocytic leukemia P388, Erlich carcinoma, ovarian tumor (ovarian carcinoma, OC), sarcoma 180 (Crocker's sarcoma, sarcoma 180, Kroker sarcoma), sarcoma 37 (sarcoma 37), and glioma 35. Tumors were transplanted intraperitoneally, subcutaneously, intramuscularly, and intracranially [13, 14]. In addition, experiments on tumor growth inhibition *in vitro* on glioblastoma 5 cell line model, the antitumor effect of dioxadet was also determined [15].

The pharmacokinetic analysis of dioxadet found that linear pharmacokinetics describe its behavior in the rat

* Currently, the regulatory and registration documentation for the drug dioxadet has expired and the drug is not produced.

body. The overall picture of activity excretion from the blood consists of three exponents, the rapid phase of excretion takes 4–6 h, and the half-life is 222 min. An important and rapid elimination route was the excretion of mono- and diethanolammonium derivatives of dioxadet, products of the ethylenimine ring opening, with bile [16]. The lipophilicity of dioxadet evidently promotes its ability to penetrate the blood–brain barrier. At 5 min after intraperitoneal administration to rats and mice, dioxadet was detected in the brain tissue and remained there for up to 72 h. At various times post-administration, the specific activity of dioxadet 14C ranged from 8% to 55% of the specific blood activity. Drug treatment in mice and rats intracranially transplanted with leukemia L1210, glioma 35, and glioma 2211 increased their life expectancy by 26%–48% [17].

The study of acute toxicity of dioxadet revealed that mice administered of lethal doses of the drug died with the phenomena of adynamia, weight loss, and moderate diarrhea. The autopsy demonstrated a sharp decrease in the thymus gland, spleen, and lymph nodes. Histological examination found hypoplasia of the bone marrow, spleen, lymph nodes, moderate dystrophic changes in the epithelium of the crypts of the duodenum and dystrophic changes in the liver. No pathological changes occurred in the heart muscle, lungs, kidneys, and stomach. Rats and mice were intraperitoneally administered with 3.8 mg/kg and 10 mg/kg of LD50 of dioxadet [18].

The result of preclinical study of dioxadet in various animal species revealed that the main dose-limiting side effect of the drug is hematopoiesis inhibition. It suppressed granulocytopoiesis and lymphopoiesis, to a lesser extent, thrombocytopoiesis. Hematopoiesis was normalized within 2–3 weeks after discontinuation of drug administration. Other side effects were not pronounced. Cardio-, pneumo-, and nephrotoxicity were not detected [19, 20].

Until 2000, phase II drug clinical trials were conducted in 15 oncological institutions in 229 patients with common forms of malignant neoplasms of various localizations. Dioxadet was used as monotherapy. Even though all patients had advanced forms of malignant neoplasms and most had previously received chemotherapy, 15.3% of patients achieved the objective therapeutic effect [11].

Clinical trials of dioxadet were conducted as an antitumor agent for chemoembolization (targeted injection of a drug into vessels directly feeding the tumor) of vessels in operable and common forms of kidney cancer in 97 patients and primary liver cancer and liver metastases of colorectal cancer in 42 patients. The effectiveness of chemoembolization with dioxadet has been proven to result in increased patient survival [5, 12, 21].

Recent studies in the field of nanotechnology have introduced new tools for the treatment of tumors into practical medicine. Nanoparticle-based complexes were used as selective tumor-specific transporters (carriers) to deliver drugs to the tumor site [22–24].

Currently, several types of therapeutic and diagnostic drugs based on highly specialized nanostructures are already used in clinical practice worldwide [25]. They were widely applied for the diagnosis and chemotherapy of malignant neoplasms, having several significant advantages over other antitumor agents. Chemotherapy with traditional cytostatic drugs often affects healthy cells in addition to tumor cells, and with the help of nanosystems, side effects occurring during its implementation can be reduced [26]. In addition, nanoobject-based drug delivery systems have controlled pharmacokinetic parameters such as clearance and distribution volume, reduced drug toxicity, increased hydrophobic drug solubility, increased drug stability (proteins, peptides, oligonucleotides), and improved biocompatibility [27]. The innovativeness of the approach depends on the creation of new nanoforms of the domestic antitumor compound, which will potentially allow targeted delivery of the drug in higher cytotoxic doses to the target cell, increase the action selectivity, and reduce the cytostatic toxicity with respect to normal cells. The main indisputable advantage of the new medicinal nanoform is the use of cytotoxic doses of chemotherapeutic drugs, which, bypassing the general blood flow, thereby exclude the general toxic effects on hematopoietic and parenchymal organs.

The current approaches to drug administration in the human body, based on the use of traditional dosage forms, have several significant drawbacks:

1. Increased consumption of medicinal substances caused by medicinal substances does not reach all the necessary biological targets or reaches, but in a concentration significantly lower than the necessary therapeutic one.

2. The non-directional effect of drugs, that is, the interaction with non-targeted biological objects, frequently leads to side effects caused by its metabolites and to inappropriate, irrational consumption of medicines.

3. Possible pronounced complications of an ongoing chemotherapeutic treatment may affect the entire course of therapy, delaying or stopping it for a certain period.

4. The inability to maintain the optimal therapeutic concentration of the drug for the required time results in the need for frequent drug administration.

5. Insufficient biocompatibility.

The most pronounced drawbacks are manifested when using medicines with a pronounced side effect. The use of nanoforms of antitumor drugs provides:

1. Prolonged effect of the drug.
2. The necessary biocompatibility.
3. Drug protection from early biodegradation.

4. Increasing the substance bioavailability with suboptimal transport properties.

5. Overcoming biological barriers, including blood–brain and blood–ophthalmic barriers, as well as better penetration through the gastrointestinal tract walls.

6. Targeted drug transport (tissue- and/or target-specific delivery).

7. Controlled drug release (reverse response, local or remote activation).

8. Maintaining the optimal therapeutic concentration of the medicinal substance.

9. Reduced side effects and systemic toxicity.

10. Possibility to visualize the focus of the pathological process, control the drug substance interaction with specific biological targets and treatment results at the cellular level.

Currently, the world pharmaceutical market has developed nanopreparations used in clinical practice [25, 28] (see the table).

Despite the large number of nanopreparations already created, this area is continuously developed. Several nanopreparations are currently used in preclinical studies and various phases of clinical trials at different centers worldwide. Simultaneously, many studies have reported that the use of targeted nanoparticles as a drug delivery system is a promising direction for the treatment of human tumors [25].

The intensive development of drug delivery systems based on micro- and nanotechnology results in not only an extension of the life of well-known medicines on the international pharmaceutical market but also the emergence of drugs with improved pharmacological and pharmacokinetic properties, which significantly expands the boundaries of their use. The development of new effective dosage forms using advanced nanotechnology has every chance to be considered one of the priorities in the field of state scientific, technical, and economic policy, contributing to:

- A significant increase in antitumor activity and a decrease in drug toxicity used in clinical practice due to targeted delivery to the tumor, prolonged action, increased therapeutic concentration, and overcoming biological barriers
- Expanding the spectrum of antitumor activity of drugs used in clinical practice and more effective treatment of tumors resistant to chemotherapy
- Development of new ways of chemotherapy — locoregional therapy and theranostics
- The closest analogs of nanodioxadet on the market today include Doxyl*, Nanoxel*, and Apealea* (micellar paclitaxel)

Doxorubicin liposomal (Doxil) for injection (2 mg/ml) is used to treat Kaposi's sarcoma, breast cancer, ovarian tumor, and other solid tumors. It exhibits less pronounced cardiotoxic, myelotoxic, and nephrotoxic effects, the "half-life" period in plasma is approximately 45 h (for free Doxyl, it is 5 min). Its disadvantage is a side effect of palmar plantar erythrodysesthesia syndrome [29, 30].

The new micellar form of paclitaxel, registered in Europe and the Russian Federation, demonstrated better tolerability compared to conventional paclitaxel and considered an increase in the safe effective dose to 250 mg/m^2, which provides a significant advantage in efficacy and progression-free survival [31, 32]. The use of the new EL cremophor-free paclitaxel is relevant in concomitant extragenital diseases (e.g., diabetes mellitus, neurologic deficits) in elderly patients and patients with allergic reactions, and sometimes in those contraindicated for additional steroids. Similar polymer micellar preparations are currently being widely investigated, and clinical data have shown a longer half-life, increased bioavailability, and reduced toxicity [33]. For example, the micellar form of paclitaxel Genexol-PM* (Samyang Pharmaceuticals, South Korea) based on a block copolymer of polyethylene glycol and lactic acid in preclinical trials indicated a concentration level in tumor tissue three times higher compared to the drug Taxol* (Bristol-Myers Squibb S. r. L., Italy) when administered intravenously and, accordingly, significantly higher efficacy in animal models of ovarian and breast cancer [34]. The drug had excellent antitumor activity and allowed the safe use of higher doses — up to 250 mg/m^2 [35].

Possible main applications of nanodioxadet

Therapeutic intraperitoneal chemotherapy for abdominal carcinomatosis of the 1st, 2nd, and subsequent lines in patients with ovarian, colon, stomach, and other primary tumors. In Russia, abdominal carcinomatosis is detected in >80,000 people per year [36]. Potentially, intraperitoneal chemotherapy is indicated for most of these patients, not conducted nowadays, but is considered one of the effective ways to increase survival.

Adjuvant intraperitoneal chemotherapy for abdominal carcinomatosis. In Russia 13,315 people had ovarian cancer for the first time, 41,154 people had colorectal cancer, and 32,031 people had gastric cancer in 2021, totaling to 86,500 people [36]. High mortality is observed in ovarian cancer in women. In 2020, 313,959 women were diagnosed with ovarian cancer worldwide, whereas 207,252 died [37]. These three tumors most frequently cause carcinomatosis of the abdominal cavity. At least a third of these patients potentially require adjuvant intraperitoneal chemotherapy, not performed at all today, which opens a new indication for a nanopreparation.

* The drug is not registered in Russia.

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Table. Nanopreparations used in the clinic

Таблица. Нанопрепараты, применяемые в клинике

Name/Manufacturer/Registration Information/ Approval	Nanocarrier/Drug	Indications	Side effects
Doxil (Caelyx) (Liposomal doxorubicin) / FDA (1995), EMA (1996), Janssen	Liposomes/doxorubicin	Breast cancer, ovarian cancer, myeloma, and Kaposi's sarcoma	Prolonged use may lead to squamous cell carcinoma of the oral cavity in women
Myocet (Liposomal doxorubicin) / EMA (2000), Teva UK	Liposomes/doxorubicin	Breast cancer	Relative instability
DaunoXome (Liposomal daunorubicin) / FDA (1996), Galen	Liposomes/daunorubicin	Kaposi's sarcoma caused by HIV infection	Cardiac side effects
DepoCyt (Liposomal cytarabine) / FDA (1999), PACIRA Pharma	Liposomes/cytarabine	Leukemia, glioblastoma, and lymphomatoid malignant meningitis	Arachnoiditis and neurotoxicity
Abraxane (Albumin-bound paclitaxel Nanoparticles) / FDA (2005), EMA (2008), ABRAXIS Bioscience	Albumin binding nanoparticles/paclitaxel	Metastatic breast cancer (secondary) and metastatic pancreatic cancer (primary)	Nonspecific binding of paclitaxel to albumin
Genexol-PM / South Korea (2007), Samyang	Polymer micelles/paclitaxel	Breast, lung, and ovarian cancer	Neuropathy, myalgia, neuropenia
Oncaspar / FDA (1994), EMA (2016), Sigma Tau	Conjugate of a drug with a polymer/L-asparaginase	Leukemia	Venous thromboembolism, pancreatitis, and hyperglycemia
Onivyde (Merrimack) (Liposomal Irinotecan) / FDA (2015), IPSEN	Liposomes/irinotecan	Metastatic pancreatic cancer (secondary)	Diarrhea, nausea, vomiting, neutropenia, and fibrillar neutropenia
Marqibo (Liposomal Vincristine) / FDA (2012), Acrotech	Liposomes/vincristine	Acute lymphoblastic leukemia with a negative Philadelphia chromosome	Drug toxicity
Eligard (Tolmar) (Leuprolide acetate and polymer; PLGH (poly (DL-Lactide-co-glycolide)) / FDA (2002), Tolmar Therap	Polymer nanoparticles/leuprolide acetate	Prostate cancer	Hot flashes followed by malaise/fatigue, dizziness, nausea, gynecomastia, and testicular atrophy
Mepact (Muramyl tripeptide phosphatidyl ethanolamine) / EMA (2009), Takeda	Liposomes/mifamurtide	Non-metastatic osteosarcoma	Chills, high fever, headache, myalgia, and fatigue
Lipusu (Liposomal paclitaxel) / EMA (2013), Luye Pharma	Liposomes/paclitaxel	Advanced stage of breast cancer, ovarian cancer, and non-small cell lung cancer	Nausea, vomiting, shortness of breath, and peripheral neuritis
Ontak (Denileukin diftitox) / FDA (1999), Eisai	A targeted drug containing interleukin-2 and diphtheria toxin	T-cell lymphoma of the skin	Allergic reactions, asthenia, nausea, vomiting (leads to dehydration in some patients), and infections
Ameluz (5-Aminolevulinic acid) / EMA (2011)	Gel containing 5-aminolevulinic acid, sodium benzoate L-α-phosphatidylcholine, and pegylated liposome	Basal cell carcinoma	Transient pain and erythema
Vyxeos (Liposomal cytarabine: daunorubicin) / FDA (2017), EMA (2018), Celator, Pharms	Liposomes/daunorubicin and cytarabine	Acute myeloid leukemia	Febrile neutropenia, fatigue, pneumonia, hypoxia, hypertension, bacteremia, and sepsis
Apealea (Polymeric micelles Paclitaxel) / EMA (2018)	Polymer micelles/paclitaxel	Cancer of the ovaries, peritoneum, and fallopian tubes	Neutropenia, diarrhea, nausea, vomiting, and peripheral neuropathy
Pazenir / EMA (2019)	Albumin binding nanoparticles/paclitaxel, infusion powder	Metastatic breast cancer, metastatic pancreatic adenocarcinoma, and non-small cell lung cancer	Side effect on healthy blood and nervous system cells
Nano-therm / EMA (2013), FDA (2018), MagForce	Fe_2O_3, superparamagnetic nanoparticles coated with aminosilane	Glioblastoma, prostate and pancreatic cancer	Moderate

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Modern nanoforms of dioxadet

Dioxadet nanoforms based on mesoporous silica particles are one of the promising nanoforms of dioxadet, because according to the literature, silica particles themselves have antitumor activities and are nontoxic [25, 28, 38–40].

Conjugates of nanodiamonds with dioxadet and doxorubicin. The study of cytotoxic properties of nanodiamond conjugates with antitumor drugs (doxorubicin and dioxadet) conducted by G.M. Berdichevsky reported that detonation nanodiamond complexes, with doxorubicin (DND–Dox) and dioxadet (DND–Diox), do not affect plasma coagulation hemostasis and functional activity of platelets and erythrocyte membrane, because they have good hemocompatibility [41].

When analyzing the effects of DND–Dox and DND–Diox on the function of mitochondria, namely, on the ATPase activity of F1F0 *Escherichia coli* (proteoliposome model) and the value of the membrane mitochondrial potential (PANC-1 cell culture model), the effect of conjugates was found to be due to the presence of DND in their composition. DND–Dox compared with DND–Diox significantly reduced the mitochondrial membrane potential, which is apparently due to the inhibitory effects of DND on the ATPase activity of F1F0 *E. coli* in combination with the Dox-dependent generation of reactive oxygen species. Understanding the role of mitochondrial dysfunction identifies the possibility of using mitochondria as targets for various types of effects, which can serve as a biochemical basis for the development of new antitumor agents. Carboxylated DND has an inhibitory effect on the ATPase activity. The doxorubicin ability to reduce the membrane potential level (model — PANC-1 cell culture) was found, without affecting the ATPase activity (model — proteoliposomes). It has been shown that DND–Diox, unlike DND–Dox, does not affect the mitochondria [42, 43].

The T98G glioblastoma cell model revealed that DND–Dox and DND–Diox demonstrate a greater cytotoxic effect on tumor cells at lower doxorubicin and dioxadet concentrations in conjugates compared with free doxorubicin and dioxadet; simultaneously, the cytotoxic effects of DND–Diox significantly exceeded DND–Dox at all studied concentrations. The obtained data revealed that DND–Diox, compared with DND–Dox, has maximum cytotoxicity with respect to glioblastoma T98G cells. The greater cytotoxicity at a lower Diox concentration in the conjugate composition compared to the individual drug makes it promising to further analyze the specific antitumor activity and acute toxicity of DHA–Diox in *in vivo* models of glioblastoma [44].

Preparation of nanogels with dioxadet. Nanocontainers used for selective drug delivery in the body and diagnosis of diseases have been investigated for a long time by many research teams [45]. Promising nanocontainers include nanogels, super-soft nanoparticles consisting of polymer hydrophilic or amphiphilic chains. Nanogels have several important properties: large loading capacity and high stability and sensitivity to small changes in the environmental conditions in which they are located (pH, ionic strength and temperature). Polymer nanogels are new biomaterials for the cancer drug delivery [46, 47].

This review aims to produce nanogels with dioxadet synthesized by cross-linked nanogels based on a block copolymer of polyethylene glycol-6-polymethacrylic acid (PEG-6-PMAC), and the study of the process introducing the antitumor drug dioxadet into nanocontainers. Our results indicated that stable nanocontainers were synthesized with a high degree of loading using the antitumor drug dioxadet [47]. The drug-loaded nanogels are directed into lysosomes, and selective toxicity to cancer cells is demonstrated [15]. The cytotoxic activity of dioxadet significantly decreased after nanogel administration. Nanogels themselves are nontoxic in the entire range of concentrations used for the treatment of nanogel-based drugs.

The cytotoxicity of the free and encapsulated form of dioxadet was examined on glioma cell lines (C6, U87) and normal cells (CHO-K1) [15]. First, it was found on CHO-K1 cells that the semi-maximal inhibition (IC50) concentration increases with decreased pH of the free dioxadet solution. This occurs because of the loss of drug activity in an acidic environment due to the discovery of ethylenimine cycles responsible for the alkylation mechanism of dioxadet. Second, cytotoxicity analysis revealed lower toxicity of dioxadet loaded into a nanocontainer compared to its free form, which can be explained by the slow drug release from the container and a lower dose interacting with cells. Doxorubicin and cisplatin had a similar decrease in cytotoxicity reported by Yokoyama et al. [48, 49]. Overall, the IC50 for all forms of dioxadet, including a free drug substance, remained high in C6 cell culture compared to doxorubicin (S. Bennis et al. [50]) or cisplatin (Y. Tokunaga et al. [51]). This effect may be generally associated with resistance of glioma C6 to dioxadeth or triazines. For example, another alkylating agent from the triazine family, temozolomide, also had a much higher IC50 for the C6 cell line and simultaneously revealed much higher toxicity against human U87 glioma cells (no data provided). However, the toxicity of free dioxadet on U87 glioblastoma cells was found to be like that of doxorubicin (Lu et al. [52]) and cisplatin (Khiati et al. [53]), but less toxic to nontumor CHO-K1 cells. In addition to the fact that this drug has low systemic toxicity and is effective against human glioblastoma cells compared to nontumor cells, making it possible to consider dioxadet as a promising chemotherapeutic drug for the treatment of brain tumors.

The efficiency of dioxadet encapsulation in containers obtained by the ordinary emulsion method. Currently, biodegradable polymer-based particles such as polymer

spheres, micelles, and polymerosomes are mostly interesting as drug delivery systems. Synthetic amphiphilic copolymers of aliphatic polyesters, such as poly (lactic acid) (PLA) or poly(e-caprolactone) (PCL) with hydrophilic polymers, have the greatest promise as biodegradable carriers to produce such particles [54]. Drug delivery systems based on amphiphilic copolymers are characterized by high bloodstream stability, biocompatibility with organs and tissues, and the ability to decompose to form nontoxic products for the body. The use of synthetic biodegradable polymers as a base for particles also make it possible to control the physicochemical properties of containers, such as size, surface properties, and decomposition rate of polymer carriers [55]. Particles based on biodegradable polymers are not toxic to cells by themselves [56].

Sinitsyna et al. [54] developed micro- and nanoparticles based on amphiphilic block copolymers of poly(ethylene glycol) with molecular weight of 5000 (PEG-5000) with poly(lactic acid) PEG5000-6-PLA and polycaprolactone PEG5000-6-PCL, capable of efficient encapsulation and controlled release of the antitumor drug dioxadet and also compared the obtained containers with carriers based on PLA and PCL homopolymers [54].

The single emulsion method allows loading more dioxadate with PMC-based particles (fine fraction) and PEG5000-6-PCL (coarse fraction). Particles based on PLA block copolymers with PEG are well suited for encapsulating small drug doses (1–3 mg). Further particle stabilization in the aqueous phase due to the hydrophilic PEG block allows loading more of the drug and preventing polymer deposition when using large molecular weights. PEG5000-6-PCL block copolymer is suitable for loading more dioxadet. Increased encapsulation efficiency and higher loaded drug compared to PEG5000-6-PLA can be explained for the amphiphilic copolymer PEG5000-6-PCL by the more hydrophobic nature of the PCL and its semi-crystalline structure, allowing more of the drug to penetrate, unlike the amorphous structure of PLA. To obtain particles from PCL and PEG5000-6-PCL, polymers with a molecular weight of <30,000 Da should be used, since due to the hydrophobic properties of the polymer, its precipitation occurs during particle formation. However, polymers with molecular weights of up to 350,000 Da can be used to achieve stable particles from PEG5000-6-PMC, which helps increase the amount of drugs loaded into the particles and is an effective tool to control the rate of drugs release into the system.

Thus, the varying nature, molecular weight, and container size of the polymer carrier are an effective tool to achieve the desired release rate. Future studies may allow the use of a combination of particles of different nature and different sizes of the drug to be dosed at the required rate for therapeutic effect in the appropriate organs.

CONCLUSION

This literature review provides data on developed nanoforms of the domestic antitumor drug dioxadet, which opens up opportunities to reduce its side effects and systemic toxicity, helps maintain optimal therapeutic concentration, increases the circulation time of the drug in the blood, and controls its release.

ADDITIONAL INFORMATION

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