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Role of New Pharmaceutical Technologies in Enhancing the Selectivity of Antitumor Drugs

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Abstract—Foreign and domestic research on nanostructured formulations of known and new anticancer drugs provide evidence in favor of improved physicochemical (solubility, stability on storage) and therapeutic characteristics (efficacy, stability in the body, selectivity of accumulation in pathological sites, toxicity) of the most part of studied formulations.

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INTRODUCTION

Chemotherapy occupies a leading place among medical technologies in oncology. The main approach to enhance the efficiency of drug therapy of malignant neoplasms consists in searching for new selective antitumor drugs and their rational formulations which would allow one to optimize procedures of drug administra-tion, develop schemes and regimes of polychemo-therapy, and improve cancer therapy [1, 2].

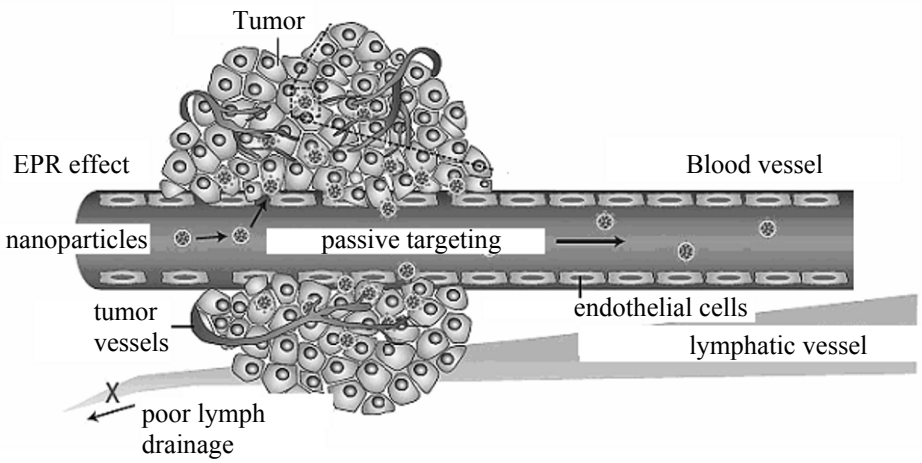
The distribution of a drug in the body depends on the physicochemical properties of the drug, as well as on the level of blood supply to one or another organ or tissue, and, therefore, the route the drug is administered defines the order of its interaction with body systems. The rate of drug entering the blood circulatory and lymphatic systems and its further distribution over organs and tissues is limited by absorption.

Most antitumor substances are chemically labile, highly toxic, and exhibit low tumor selectivity, which generates a demand to increase the level of accumulation of the active substances in tumor tissues. As known, direct drug injection into a diseased tissue give no positive results, even though some examples of successful use of implanted drug formulations for local drug delivery into voids and removed tumor bed have been reported. However, the extremely low drug concentrations in systemic circulation make such formulations inefficient in the treatment of metastatic lesions. Thus, one of the reasons for the inefficiency of antitumor drugs is their nonspecific body distribution: Not infrequently less than 1% of the injected drug dose reaches the tumor site.

Physiological Features of Tumor Tissue, Ensuring Efficiency of Nanosized Drug Delivery Systems

The tumor tissue features a vigorous angiogenesis, viz. the physiological process through which new blood vessels form from pre-existing ones. Under normal conditions, this process is observed in inflammation, tissue regeneration, and wound healing. Atypical angiogenesis is associated with most pathological states, including vascular malformation, atherosclerosis, obesity, as well as cancer [3]. The development of capillary network plays a key role in the transformation of a small tumor lacking its own vascular network into a larger, well vascularized tumor. Once a tumor has become larger than 1–2 mm, it starts to need an independent blood circulation. In this connection angiogenesis plays a key role in tumor growth and metastasis [4–7].

The physiological and morphological characteristics of blood vessels of solid tumors are much different from those in a healthy tissue [8]. Just such an abnormal structure of tumor vessels allows nanosized drug delivery systems to be used for enhancing the efficiency of treatment of malignant tumors. Nanoparticles are capable of penetrating through capillary pores of diseased areas, where microvasculature vessels are perforated and have pores



Schematic presentation of the EPR effect in tumor vessels.

0.4–0.6 μm in size. This phenomenon was defined as the EPR (Enhanced Permeability and Retention) effect (see figure). Due to this effect, conditions are created for transfer of antitumor drug carriers from the bloodstream to diseased tissues [9]. In the norm, this phenomenon does not take place, because nanosized drug carriers are larger than capillary pores in healthy vessels. Furthermore, tumor tissues feature disturbed lymphatic drainage. This phenomenon favors retention of nanosized drug carriers and accumulation of the drug in the malignant tumor, thus enhancing the efficiency of drug therapy [10].

One of the ways to improved selectivity of antitumor active substances is associated with the development of pharmaceutical technologies for manufacture of nanostructured drug delivery systems. At present the most popular antitumor drug carriers are liposomes, micelles, nanoemulsions, etc. [11]. For a more efficient passive transport into tumors, nanoparticles are modified by amphiphilic surfactants. Such modification prevents nanoparticles from being entrapped by liver and spleen macrophages, i.e. favors their distribution beyond the reticuloendothelial system [12].

Liposomal Antitumor Formulations

The encapsulation of drugs in vesicles (liposomes) prolongs their circulation in blood and enhances the efficiency of their accumulation in the tumor tissue, which protects the active substances from metabolic degradation and prevents changes in their tissue distribution, specifically, increased accumulation in organs rich in mononuclear phagocytes, liver, spleen, and bone marrow and reduced accumulation in kidney, myocardium, and brain [13–15].

Loposomes can be used to transport both hydrophilic and hydrophobic drugs [16, 17]. The composition, surface charge, and size of lipids determine their physicochemical and biopharmaceutical characteristics, such as the rate of clearance from the injection site and blood plasma and the rate of delivery to a target organ. Liposomes with different lipid compositions can encapsulate different quantities of active substance, and, therewith, the encapsulation degree depends on the structure, size, charge, and lipid composition of lipo-somes, as well as on the intrinsic physicochemical characteristics of active substances.

A liposome-encapsulated substance is protected from enzymes, which makes more efficient medicines susceptible to biodegradation in biological fluids. Liposomal formulations scarcely penetrate into myocardium and skeletal muscles, probably due to a peculiar structure of the endothelium of these organs. Liposomes do not come into the excretory system and, therefore, do not undergo glomerular filtration. The encapsulation in liposomes affects the pharmacokinetics of substances, specifically, the rates of their clearance from the injection site and blood, organ and tissue distribution and redistribution, and targeting efficiency. Since liposomes decrease toxicity of their encapsulated drug, the dose of the latter can be increased without evident side effects. As a result, cancer therapy could be brought to a qualitatively higher level [18].

The effort of many researchers is presently being focused on increasing the safety of efficient anticancer anthracycline antibiotics (doxorubicin [19], daunorubicin [20]), which cause severe side effects. The encapsulation in liposome carriers reduced the cardiotoxicity of these drugs and increased the survival rate of experimental animals compared to the control group administered free drugs [21, 22]. The efficiency of anthracyclines is enhanced by their encapsulation in phospholipid vesicles with a high cholesterol content in the lipid bilayer or in phospholipids with a high-temperature phase transition, which favor retention of drugs in liposomes when they enter the blood stream.

The first liposomal formulations approved for clinical use were 80–200-nm cholesterol-containing phospholipid vesicles capable, to a greater or lesser extent, of slipping away from reticuloendothelial cells. Such liposomal formulations include Ambisome (liposomal amphotericin), Myocet (liposomal doxorubicin [23]), Daunoxome (liposomal daunorubicin [24]). The incorporation into liposomes of lipids with different physicochemical properties made it possible to develop liposomal formulations of vincristine [25], vinorelbin [26], topotecan [27], lurtotecan [28], mitoxantron [29], paclitaxel [30], irinotecan [31], etc.

Technologies of manufacture were developed, which allow prolongation of the circulation time of liposomes and their targeted delivery beyond the reticuloendothelial system. As a breakthrough achievement we could mention the development of Doxil which represents doxorubicin hydrochloride–loaded liposomes (80–120 nm) comprising phosphatidylcholine, cholesterol, and a conjugate of dipalmitoyl phosphatidylethanolamine and PEG-2000 as steric stabilizer (Stealth liposomes). Other liposomal doxorubicin formulations include Caelyx and Lipidox fabricated from a high-purity egg phosphatidyl-choline (liposome size ca.150 nm), as well as Myocet, a doxorubicin–citrate complex (120–150 nm) [32]. The mentioned liposome formulations exhibit a potent antitumor and antileukemia activity, they allow free release of doxorubicin from liposomes and its local distribution in tissues and organs, thus reducing toxicity of the antibiotic. The liposomal forms of doxorubicin exhibit much lower cardiotoxicity, myelo and immune suppression, and longer circulation times than the free form of the drug. They are applied in the therapy of soft tissue sarcoma, lung and breast cancer, as well as thyroid, pancreatic, kidney, ovarian, uterine, and other cancers. With liposomal formulations, a lower rate of general toxic reactions, such as edema, vomiting, alopecia, etc., were observed.

Over the past years the development of liposomal formulations of such antitumor drugs as Irinotecan, platinum derivatives, paclitaxel, etc., has been reported.

Irinotecan hydrochloride is a water-soluble derivative of camptothecin whose active metabolite SN-38 shows a high antitumor activity [33]. Polyethylene glycol–modified liposomes (PEG-liposomes) containing irinotecan were found to efficiently treat colon and small-cell lung cancer [34]. Animal tests provided evidence to show that liposome-encapsulated irinotecan prolongs the lifespan of animals compared to those treated with a free drug [35].

The observed failures to treat oncological patients with platinum chemotherapeutics are associated with the following reasons: Expressed toxicity of such drugs (nephro-, oto-, and neurotoxicity), as well as chemoresistance of malignant neoplasms. Liposomal formulations are free of these disadvantages: They differ from the original platinum drugs in the way they are delivered to a target cell, body and tissue pharmaco kinetics and distribution, low toxicity, and high efficiency.

The toxicity and antitumor activity study of liposome-encapsulated platinum compounds on mice with leukemia and reticulosarcoma in [36] showed the tested formulations all exhibit a higher antitumor and a lower nephrotoxicity compared to free drugs. After intravenous injection of a free platinum drug, 35.7% of experimental animals died from general toxic effects, whereas with liposomal platinum formulations, no animals died, and their body weight almost did not change. Tumor growth in animals treated with the liposomal formulation was three times slower than in control animals, and their lifespan increased by 91.5%, on average. It was established in animal experiments that the maximum dose of the liposomal platinum formulation (Lipoplatin), at which no animals died and no pathologies in visceral organs was observed, was 10.0 mg/kg, whereas the respective value for the free cisplatin was 7.5 mg/kg. The LD_{100} doses for the liposomal and free forms were 50.0 and 30.0 mg/kg, respectively. Clinical trials of Lipoplatin in patients with III–IV-stage ovarian cancer and its relapses showed that this formulation is efficient against tumors resistant to cisplatin [37].

A liposomal paclitaxel formulation shows a similar therapeutic efficiency and reduced toxicity, as well as

enhanced tolerability than an intravenous Paclitaxel formulation [38].

Micellar Antitumor Formulations

Micelles are colloid particles up to 50 nm in size, which have a hydrophobic core and a hydrophilic shell. Drug substances can either be encapsulated in the core of a micelle or covalently bind to its surface. Various modifications of micelle shells are proposed, which make them more thermodynamically stable and biocompatible, thereby prolonging the circulation time of micelles [10].

Of the greatest use in medicine are polymer micelles with a core which represents the hydrophobic part of a block copolymer is capable of encapsulating a water-insoluble drug, while the outer shell of the block copolymer protects the drug from water and stabilizes micelles, preventing them from being entrapped by reticuloendothelial cells [39, 40]. Like liposomes, micelles can be used for targeted drug delivery. To this end, certain elements sensitive, say, to pH are anchored on micelle surface [41]. At present synthetic approaches to polymer micelles to be used as carriers of such antitumor drugs as paclitaxel, taxol, adriamycin, etc., are being developed [42].

Micellar paclitaxel and camptothecin are better soluble and exhibit a higher antitumor activity that the free forms of the drugs. Thus, the solubility of the hydrophobic cytostatic paclitaxel encapsulated in micelles on the basis of PEG and phosphatidyl ethanolamine in water reaches 5 mg/mL against 0.3 μg/mL for free paclitaxel [43]. Comparative cytotoxicity study of Taxol (paclitaxel dissolved in Cremophore ELP, a complex solvent on the basis of polyoxyethylated castor oil) and micellar paclitaxel on non-small-cell lung, breast, and ovarian cancer cells revealed similar efficiencies of these two dosage forms. Moreover, both *in vivo* and *in vitro* experiments established that micellar paclitaxel is nontoxic [44].

South Korean researchers developed a micellar form of paclitaxel on the basis of a PEG–lactic acid block copymer (Genexol) [45]. Clinical trials showed that this formulation is more efficient and less toxic than Taxol: The maximum tolerable dose (MTD) of Genexol was estimated at 390 mg/m^2. Genexol is presently under clinical trials against breast cancer and non-small-cell lung cancer and, in combination with Cisplatin, against gastric cancer [46].

Using 80-nm micelles Japanese researchers developed a micellar paclitaxel formulation NK105. The area under the pharmacological curve constructed in the clinical trial of this formulation at a dose of 180 mg/kg in patients with solid tumors was 450 μg h/mL (blood concentration after single injection), which is higher by an order of magnitude compared the respective value for Taxol [47].

Research on the encapsulation of doxorubicin in polymer micelles on the basis of Pluronic block copolymer [48] and of camptothecin in PEG-β-poly(β-benzyl-L-aspartate) micelles [49]. All the developed micellar antitumor formulations are under preclinical and clinical trials.

Nanostructured Antitumor Formulations

Along with liposomes and micelles, a growing number of uses in nano-oncology are being found for nanosized delivery systems which ensure selective drug accumulation in tumor. These systems function due to the physiological mechanisms of transport, specific for endogenous substances. For example, new paclitaxel formulations on the basis of human albumin (Abraxane, USA), a long-chain fatty acid (Taxoprexin, USA), and polyglutamic acid (Xyotax, USA) were developed.

Abraxane is a drug formulation in which the hydrophobic paclitaxel in encapsulated in 130-nm albumin nanoparticles. After intravenous injection such loaded particles rapidly dissociate to form individual albumin–paclitaxel complexes, and drug targeting to tumor cells is provided not only due to the EPR effect but also due to an albumin-specific mechanism (endothelial transcytosis through the albumin gp60 receptor and osteonectin-mediated internalization of the albumin–drug complex in tumor cells. Clinical trials of Abraxane showed that its MTD (300 mg/m^2) is double that for Taxol. The dose-limiting factors were side effects with respect to the hematopoietic system, which are characteristic of paclitaxel in itself; as a result, the infusion time could be reduced to 30 min [50, 51]. In view of its confirmed high clinical efficiency, in 2007 Abraxane was registered by the FDA.

Taxoprexin, a conjugate of paclitaxel with docosohexaenoic acid (a long-chain fatty acid) which is a component of food lipids, is presently under clinical trials. The cytostatic effect of paclitaxel in this dosage form reveals itself upon cleavage of the fatty acid, taking place directly in tumor cells. As a result, the MTD of paclitaxel in patients with solid tumors reached 1100 mg/m^2 [52].

A macromolecular complex of paclitaxel with polyglutamic acid (MW 40–50 kDa) was developed (Xyotax). Its accumulation in tumor is due to the EPR effect, whereas intracellular transport to tumor cells is provided by efficient endocytosis not involving P-glycoprotein. The antitumor effect of Xyotax reveals itself directly in tumor cells due to gradual release of paclitaxel due to protolytic hydrolysis of the complex. This new formulation is water-soluble and allows the infusion time to be reduced to 10–20 min. Xyotax is presently under Phase III clinical trials and expected to be approved for lung and ovarian cancer therapy [53].

Nanosized Delivery Systems Developed at the Blokhin Cancer Research Center, Russian Academy of Medical Sciences

The Laboratory of Drug Development, Research Institute of Experimental Diagnosis and Therapy of Tumors, Blokhin RCRC RAMS, is developing liposomal drug formulations with the aim to enhance the efficiency of known and new anticancer drugs.

Clinical oncology presently makes an extensive use of photodynamic therapy, a technique which employs light-sensitive substances (photosensitizing agents). For more efficient therapy and lower phototoxicity for healthy tissues, liposomal formulations of photosensitizing agents are being developed [54, 55]. The encapsulation in liposomes allowed improvement of the therapeutic efficiency of such known photosensitizers as photoditazin and photosens, as well as ensure efficiency of newly synthesized photoactive substances, in particular, tiosens.

Photoditazin is an efficient photosensitizing agent containing a composition of three chlorin tetrapyrroles (with a hydrogenated ring D), the most abundant of which (80–90%) is chlorin-e_6. The agent, being excited with light with a wavelength of 654–670 nm, can destroy biological substrates. It exhibits a high phototoxicity, on account of a high quantum yield of singlet oxygen. Polyethyleneglycol-modified liposomal photoditazin shows a lower phototoxicity for healthy tissues compared to an injection dosage form of this agent; an optimal composition and technology for manufacture of lipo-somes with an average diameter of 165 nm. The efficiency of liposome-encapsulated photoditazin is 91% [56]. Tests on animals with induced Ehrlich cancer showed that the liposomal photoditazin formulation is 15–20% more selectively accumulated in tumor compared to the aqueous solution, and the efficiency of treatment increased from 0 to 40% [57].

Photosens (synthesized at the NIOPIK State Research Center) is aluminum phthalocyanine sulfate. This product shows intense absorption in the red spectral region at 675 nm. At present photosens is produced in Russia as a concentrate for solution for infusion, which is used to treat light forms of lip, throat, and tongue cancer, as well as primary lung cancer.

The Blokhin RCRC RAMS developed a liposomal photosens formulation with a particle size of no less than 180 nm and ≥80% of the drug incorporated in the aqueous phase of liposomes [58]. Liposomal photosens exhibits phototoxicity with respect to finite cell lines, killing 60–80% of cells. The accumulation level of liposomal photosens on mouse skin after injection in a therapeutic dose of 2 mg/kg is 3 times lower than the accumulation level of a 0.2% solution of photosens at a therapeutic dose of 4 mg/kg [59]. It was found that the efficiency of photoditazin with liposomal photosens at a therapeutic dose of 2 mg/kg in solid tumor therapy compares with the antitumor activity of a 0.2% photosens solution at a therapeutic dose of 4 mg/kg. Thus, the use of liposomal photosens makes it possible to reduce the therapeutic dose and dermal phototoxicity.

Tiosens is a domestic infrared phosphosensitizing agent synthesized at the NIOPIK State Research Center and presently undergoing clinical trials at the Blokhin RCRC RAMS. To increase the solubility of tiosens and increase its accumulation selectivity, a liposomal dosage form of the agent was developed; its optimal composition was established and manufacture technology was proposed [60]. Assessment of the photodynamic activity of tiosens in this formulation by the tumor growth suppression criterion in animal experiments revealed the highest responses in Ehrlich tumor (tumor growth suppression 76%), solid variant of p388 lymphocytic leukemia (76%), and sarcoma 37; in the last case, high growth suppression (94%) was associated with recovery of 33.3% of experimental animals [61, 62].

Nanostructured liposomal forms were used to reduce the toxic effects of high-activity antitumor drugs on the basis of alkylnitrosourea derivatives (lysomustine), bis(β-chloroethyl)amine (cyfelin, Sarcolysin), and anthracycline antibiotics (doxorubicin).

The Blokhin RCRC RAMS previously developed a unique formulation “Lysomustin Lyophilisate for Solution for Injections” which showed efficacy in

monotherapy of skin melanoma and lung cancer; however, at Phase III clinical trials this formulation exhibited high toxicity, and, therefore, its practical use was suspended [63]. To ensure selective action on tumor cells and reduce toxicity, an attempt was undertaken to develop a nanostructured drug formulation in the form of sterically stabilized liposomes. As shown in experimental models of tumor growth (L-1210 leukemia and Lewis lung carcinoma), lysomustin in the new formulation is more bioavailable, shows an extended range of full recovery doses (125–225 mg/kg), and gets less toxic [64, 65].

The cyfelin and Sarcolysin substances synthesized at the Blokhin RCRC RAMS exhibited a high cyto-static effect in patients with myeloma, gonioma, reticulosarcoma, endothelioma, and Ewing sarcoma [66]. However, the applicability of these substances is limited by their low bioavailability, as well as by the hydrophobicity of cyfelin and hematotoxicity of sarcolysin. Liposomal dispersions of cyfelin and sarcolysin, containing 98% and 62% of the active ingredient, respectively, are free of these drawbacks.

To obtain evidence for the advantage of liposomal formulation, their cytostatic effect was studied in comparison with free cyfelin and sarcolysin substances. The new formulations showed high activity in *in vitro* experiments on human tumor cell lines. The cytotoxicity of liposomal cyfelin and sarcolysin differed from that of the free substances by 33 and 11%, respectively, in the case of SKOV-3 ovarian carcinoma cells and by 34 and 3%, respectively, in the case of Jurkat T-cell lymphoblastic lymphoma cells. Thus, liposomal cyfelin is equally active against both cancer cell lines, whereas liposomal sarcolysin is more efficient against the first of the two human tumors.

For a more selective release of the antitumor anthracycline antibiotic doxorubicin, the composition of the thermoliposomal doxorubicin formulation was optimized, and the technology ensuring production of liposomes with a particle size of 170 nm and efficient (87–94%) encapsulation of the drug in freshly produced vesicles was scaled-up. Along with accelerated drug release from liposomes, local hyperthermy favors more rapid blood circulation in tumor and penetration of liposomes into tumor [67]. Preclinical trials showed that the “Doxorubicin Thermoliposomal, Lyophilisate for Solution for Injections 0.7 mg” in combination with local hyperthermy acts more selectively and is less toxic than free doxorubicin [68].

CONCLUSIONS

Even though modern oncology has made undeniable progress, the problem of enhancing efficiency of therapy of malignant neoplasms still remains extremely urgent. One of the most promising directions in the discovery of new-generation drugs is associated with the development of nanosized delivery systems on the basis of liposomes and micelles.

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