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REVIEW ARTICLE

Anticancer Drug Delivery: An Update on Clinically Applied Nanotherapeutics

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Abstract The development of chemotherapy using conventional anticancer drugs has been hindered due to several drawbacks related to their poor water solubility and poor pharmacokinetics, leading to severe adverse side effects and multidrug resistance in patients. Nanocarriers were developed to palliate these problems by improving drug delivery, opening the era of nanomedicine in oncology. Liposomes have been by far the most used nanovectors for drug delivery, with liposomal doxorubicin receiving US FDA approval as early as 1995. Antibody drug conjugates and promising drug delivery systems based on a natural polymer, such as albumin, or a synthetic polymer, are currently undergoing advanced clinical trials or have received approval for clinical applications. However, despite attractive results being obtained in preclinical studies, many well-designed nanodrugs fell short of expectations when tested in patients, evidencing the gap between nanoparticle design and their clinical translation. The aim of this review is to evaluate the extent of nanotherapeutics used in oncology by providing an insight into the most successful concepts. The reasons that prevent nanodrugs from expanding to clinic are discussed, and the efforts that must be taken to take full advantage of the great potential of nanomedicine are highlighted.

Key Points

Nanomedicine is an attractive option to palliate the shortcomings of chemotherapy, including severe adverse side effects and multidrug resistance.

Pre-clinical knowledge and clinical expertise are progressing to extend nanotherapeutics in oncology.

1 Introduction

Due to its localization and stage of severity, cancer variability highlights the need for specific and effective treatment for patients. Historically, antineoplastic agents are low-weight molecules that have been developed since the 1940s and that have enabled progress in cancer management, gradually introducing the concept of chemotherapy and the possibility of efficiently treating patients with chemical drugs initially considered as poisons [1]. The first molecule to be synthesized was cyclophosphamide, a nitrogen mustard derivative used in 1943 for lymphomas that induced DNA structural modifications by alkylation [2]. The main molecules still in use today were synthesized during the following 25 years (Table 1). By their mode of action, they target fundamental constituents of malignant cells and thereby have been successfully used to treat malignancies. Treatment efficacy has been reinforced by the simultaneous or sequential administration of chemotherapeutic agents in order to overcome drug

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Table 1 Main antitumor chemical discoveries and their mechanism of action

Molecule	Mode of action	Target	Date of discovery or testing
Cyclophosphamide	Alkylating agent	DNA	1943
Methotrexate	Folic acid antagonist	Antimetabolite	1948
6-Mercaptopurine	Purine analog	Antimetabolite	1954
5-Fluorouracil	Pyrimidine analog	Antimetabolite	1957
Vinca alkaloids	Spindle poison	Tubulin	1963
Taxanes	Spindle poison	Microtubules	1967
Doxorubicin	Intercalating agent	DNA	1969
Cis-platin	Formation of DNA adducts	DNA	1969

resistance while limiting adverse side effects. For instance, FEC protocol [5-fluorouracil, epirubicin (anthracycline), cyclophosphamide] used for node-positive breast cancer has been tailored with docetaxel (taxane) [3]. Nonetheless, several drawbacks were highlighted. Poor water solubility, poor pharmacokinetics, and adverse side effects have contributed to limit the clinical applications of many low-weight molecular drugs with potential antineoplasic properties. Only 5 % reach the clinical trial stage and, in this case, the combination with other chemotherapies results in cumulative toxicities that constitute a major hindrance to the treatment of patients [4]. For example, the cumulative dose-related cardiotoxicity limits the use of anthracyclines in chemotherapeutic regimens [5]. Another aspect to consider is the difficulty for therapeutic drugs to distribute throughout the tumor. The disorganized structure of solid tumors includes abnormal blood vessel architecture and function that restrict drug delivery to the central part of the tumor. In addition, the lack of lymphatic vessels contributes to increase the tumor interstitial fluid pressure (IFP). Uniform elevation of IFP results in a reduced flow of the drug from the vessels, leading to poor drug distribution. Intrinsic resistance to anticancer drugs has been complicated by acquired multidrug resistance (MDR) that constitutes a major obstacle in chemotherapy. MDR includes several cell mutations following repeated drug courses, with, as a result, the efflux of drugs from the cell or the increase in drug detoxification. In both cases, the cell sensitivity to drug-induced cell death mechanisms such as apoptosis is hampered and therefore requires the use of noncross-resistant chemotherapeutic agents [6].

To improve the properties of existing antitumor agents, the concept of nanocarriers vectorizing anticancer drugs has been developed, ushering in the era of nanomedicines. A recent extensive review identifies approximately 100 nanocarriers, most of which have been evaluated in phase I or II clinical trials in cancer patients [7]. This paper provides an overview on the clinical use of nanotherapeutics in oncology, focusing on the most successful concepts along with the reasons that restrict the expansion of nanomedicine to clinics.

2 Definition of Nanomedicine

The field of nanomedicine addresses medically related nanotechnologies based on a patient-centric approach. In 2004, the European Science Foundation (ESF) established a consensus on a relatively simple definition of nanomedicine: "Nanomedicine uses nano-sized tools for prevention, diagnosis and treatment of disease and to gain increased understanding of the complex underlying pathophysiology of disease. The ultimate goal is improved quality-of-life" [8].

Considering the evolution of the chemical cancer treatments, nanomedicine represents a growing field offering more and more therapeutic prospects against cancer. Therefore, it is difficult to provide a clear definition of nanopharmaceuticals and no consensus has yet been reached regarding what can or cannot be within the scope of nanomedicines. The ESF conference noted that "nanopharmaceuticals can be developed either as drug delivery systems or biologically active drug products", and defined nanopharmaceuticals as "nanometer size scale complex systems, consisting of at least two components, one of which is the active ingredient" [8].

Far from perfect, the above terminology confers nanopharmaceuticals (drugs and drug delivery systems) either to relatively simple conjugates, such as drugs embedded in liposomes, or much more sophisticated conjugates, as multifunctional platforms containing drugs, proteins, or genes combined with targeting agents enabling in vivo detection.

3 From Bench to Bedside

Recently, the review by Duncan and Gaspar [9] explored all facets of nanomedicine development, including the issue of tumor targeting, which was particularly discussed. The US National Institute of Health database (http://www.clinicaltrials.gov), which registers clinical studies conducted around the world, currently reveals 145 clinical studies for the terms 'nanoparticles' and 'cancer'. This low

number, compared with the 45,139 clinical studies in oncology registered by the website, clearly shows the gap between nanoparticle design, quoting more than 9000 publications in the US National Library of Medicine's PubMed, and clinical translation. The hope raised by promising preclinical studies has often resulted in disappointment when nanomedicines have been applied in patients. This may be related to inappropriate preclinical or clinical methodologies, but the real shortcoming could be the lack of precise understanding of elements that govern passive and active (or receptor-mediated) targeting. Undoubtedly, tumor angiogenesis, through the formation of leaky neovessels, facilitates nanoparticle access to the tumor, and the impairment of lymphatic drainage contributes to maintain them inside the tumor. These tumor characteristics established the basis of the enhanced permeability and retention (EPR) effect, a concept that appeared approximately 30 years ago [10]. Since then, the factors that influence both the angiogenesis and EPR effect have been extensively studied, showing the complexity of angiogenic vasculature and the limitation of the EPR effect [11–13]. The latter issue was widely discussed in a recent workshop organized by the Alliance in Nanotechnology in Cancer (October 2012), from which it has emerged that the heterogeneity of EPR in tumors is a crucial point that requires evaluation in patients [14]. Imaging methods to evaluate EPR-mediated drug released into the tumor could prove very informative but remains poorly documented in patients [15]. An interesting strategy could be enhancement of the EPR effect by means of drugs that impact vascular effectors involved in IFP or vessel wall permeability [14]. An example is given by angiotensin II-induced high blood pressure to improve drug delivery by pushing the drug into the tumor interstitium [11]. Positive results have been already obtained in patients but need to be confirmed [11, 14]. In addition to the EPR effect, active targeting, essentially based on receptor overexpression at the tumor cell surface, is complicated by several parameters, depending on receptor functionality, their density at the cell surface, and kinetics of dose-dependent receptor saturation. Such information, which is not easily accessible with imaging and molecular analysis, is rarely taken into account for the design of clinical protocols. Receptor-mediated transcytosis to facilitate the entry of nanoparticles across the blood–brain barrier (BBB) is another aspect of active targeting. Endothelial cells of the BBB possess transporter systems such as the glucose transporter, or receptors such as insulin or transferrin receptors. Via its ligand diferric transferrin, the transferring receptor promotes iron delivery to the brain. By using this modality of molecule transfer, transferrin receptor-binding nanoparticles are able to cross the BBB and to deliver their payload to brain tumors. This strategy of gene therapy is currently being evaluated for recurrent glioblastoma in a phase II trial for delivering the wild-type p53 gene to sensitize the tumor to chemotherapy [16].

As highlighted by Duncan and Gaspar, appropriate prognostic indicators remain a key issue to the identification of patients, who are supposed to benefit from tumor targeting treatments [9]. For instance, paclitaxel poliglumex (PPX; CT-2103), a biodegradable polyglutamate-Taxol® conjugate, initially disappointing in a phase III study completed for lung cancer, showed increased survival in women but not in men when data were further carefully analyzed. This gender-dependent response was attributed to the correlation between estrogen levels and cathepsin B activity, the latter being closely related to taxol release from polymeric conjugate [17]. Finally, Cathepsin B activity and estradiol levels were regarded as potential biomarkers to predict treatment efficacy [18].

Nevertheless, some nanomedicines have already come into clinical use and others continuously enter into clinical trials. The paragraphs below, together with a simplified scheme (Fig. 1), give an overview of the clinically available nanodrug delivery systems according to their chemical structure.

4 Classification of Nanotherapeutics

Several nanoconstructions have been investigated regarding anticancer drug delivery, most of which develop concepts based on lipid or polymer structures. The first category is essentially represented by liposomes, spherical structures ranging from 100 to 400 nm in size, whereas the second category is more heterogeneous with a variety of smaller (≤100 nm) polymer-based chemical entities. Furthermore, specific structures such as albumin-bound nanoparticles or antibody–drug conjugates (ADCs) are also promising nanomedicines. All nanotherapeutics approved for clinical use or subjected to advanced clinical trials are listed in Table 2.

4.1 Liposomes

Constituted by an aqueous core surrounded by one or several phospholipid bilayers, liposomes are biocompatible and biodegradable entities able to entrap hydrophilic drugs into their cavity, while allowing water insoluble drugs to be inserted into the lipid bilayers. According to the number and size of lipid bilayers, liposomes can be constituted of small unilamellar vesicles, large unilamellar vesicles, or multilamellar vesicles [19]. The concept was invented in the late 1960s and since then the design of liposomes to achieve delivery of poorly soluble small molecules while controlling their toxicity has continuously evolved [20].

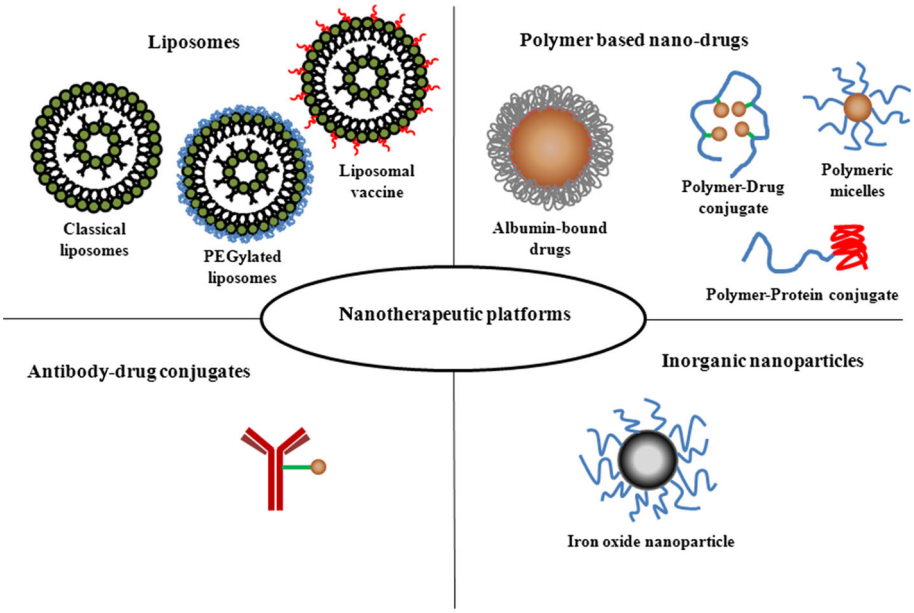

Fig. 1 Schematic illustration of targeted drug delivery systems used in clinical cancer care

Drug loading into the liposomes and monitoring of the drug release rate is now achievable and the lack of stability of conventional liposomes, due to their interception by the immune system, has been minimized by PEGylation of the liposome surface [20, 21]. PEGylated molecules have the main advantage of avoiding opsonization and destruction by reticuloendothelial system (RES) agents (hepatocytes and Kupffer cells), offering an increased circulation time. When compared with conventional liposomes, PEGylated counterparts show increased half-life, decreased plasma clearance and distribution volume, along with better accumulation in tumors (reviewed by Milla et al. [21]). Nevertheless, albeit the increasing number of liposomal formulations of anticancer agents entered into clinical trials, few of them have been granted approval for cancer treatment [22].

Liposomal doxorubicin is the best known example and to date remains the reference in clinical practice. Because liposomal doxorubicin was proven effective in the reduction of cardiotoxicity, PEGylated liposomal doxorubicin [PLD; Caelyx®, Doxil® (Johnson & Johnson); Lipo-Dox® (Taiwan Liposome)] has been approved for Karposi's sarcoma, ovarian cancer, and multiple myeloma, as well as for metastatic breast cancer (MBC), in Europe (EU) [23, 24]. Non-PLD [Myocet® (Cephalon)] has been granted approval in the EU and Canada for MBC treatment in combination with cyclophosphamide [25]. Liposomal doxorubicin formulations are presumed to provide drug accumulation at tumor sites because liposomes easily exit from the bloodstream through leaky neovasculature. In healthy tissue, such as the heart, endothelial junctions are tightly maintained and therefore liposomes do not readily exit the circulation. When compared with conventional doxorubicin, non-PLD and PLD display considerably slower clearance from blood circulation, although non-PEGylated liposomes are phagocytized by mononuclear cells [22]. Compared with other monotherapies, PLD has proven to be similarly efficient but less cardio- and hematologically toxic, although inducing cutaneous reaction due to PLD accumulation in the skin. With Myocet®, skin adverse effects have been rarely observed; however, severe hematological toxicity was registered and was attributed to the higher doses delivered compared with those commonly used in clinical practice [25].

Aside from the other four liposomal anticancer drugs—daunorubicin [DaunoXome® (Galen)], cytarabine [DepoCyt® (Pacira)], vincristine sulfate [Marqibo® (Talon)] and the immunomodulator mifamurtide [Mepact® (Takeda)], approved for more restricted indications (Karposi's sarcoma [26], lymphomatous meningitis [27], acute lymphoblastic leukemia (ALL) [28], and children osteosarcoma [29], respectively)—many anticancer agents embedded in liposomes have been subjected to clinical trials [22]. Among them, the only ones to reach phase III clinical trial are Lipoplatin, a liposomal formulation of cisplatin developed by Regulon for non-small cell lung cancer (NSCLC) [30], and irinotecan (CPT-11) nanoliposomes [MM-398; PEP02 (Merrimack)] for metastatic pancreatic cancer [31]. Overall, most of these liposomal formulations were characterized by better tolerability when compared with the free drug; however, their efficacy was expected to be far higher. One of the reasons accounting for this lesser efficacy could be the difficulty for the embedded drug to be released into cells at/or near its site of

Table 2 Nanotherapeutics approved for clinical use or being evaluated in phase III clinical trials

Category	Agent	Status	Indications	References
Liposomes	*Doxorubicin*	*Approved*		
	Doxil® (US)	FDA 1995	Karposi's sarcoma	[22]
		1999	Ovarian cancer	
		2007	Multiple myeloma	
	Caelyx® (EU)	EU 1996	Karposi's sarcoma, multiple myeloma, breast and ovarian cancer	[22]
	Lipo-Dox®	Taiwan 2002	Karposi's sarcoma, breast and ovarian cancer	[23]
	Myocet®	EU 2000	Breast cancer (cyclophosphamide)	[24]
		Canada 2001		
	Daunorubicin	*Approved*		
	DaunoXome®	1996	Karposi's sarcoma	[25]
	Cytarabine	*Approved*		
	DepoCyt®	1996	Lymphomatous meningitis	[26]
	Vincristine	*Approved*		
	Marqibo®	FDA 2012	ALL	[27]
	Muramyl dipeptide	*Approved*		
	Mepact®	EU 2009	Osteosarcoma	[28]
	Cisplatin			
	LipoPlatin®	Phase III	NSCLC	[29]
	Irinotecan			
	MM-398 (PEP02)	Phase III	Pancreatic cancer	[30]
Thermosensitive	*Doxorubicin*			
liposomes	ThermoDox®	Phase III	Hepatocellular carcinoma	[36]
Liposomal vaccine	*Lipopeptide*			
	Tecemotide (L-BLP25)	Phase III	Stage III NSCLC	[35]
Polymers				
Drug-conjugates	*Irinotecan*			
	NKTR-102/Etirinotecan pegol	Phase III	Breast cancer	[40]
	Paclitaxel			
	Paclitaxel poliglumex (PPX)	Phase III	NSCLC	[42]
Protein-conjugates	*SMANCS*	*Approved*		
	Zinostatin stimalamer®	Japan 1994	Hepatocellular carcinoma	[46]
	l-Asparaginase	*Approved*		
	Oncaspar®	2006	ALL	[48]
Micelles	*Paclitaxel*	*Approved*		
	Genexol-PM®	South Korea 2007	Breast cancer	[53]
	Paclical®	Phase III	Ovarian cancer	[7]
	Doxorubicin			
	Livatag®	Phase III	Hepatocellular carcinoma	[54]
Albumin-bound nanoparticles	*Paclitaxel*	*Approved*		
	Abraxane®	2005	Breast cancer	[55]
		2012	NSCLC	
		2013	Pancreatic cancer	
Inorganic nanoparticles	*Iron oxide*	*Approved*		
	NanoTherm®	EU 2010	Glioblastoma	[61]

Table 2 continued

Category	Agent	Status	Indications	References
Antibody–drug conjugates	*Emtansine/trastuzumab*	*Approved*		
	Kadcyla® (ado-trastuzumab emtansine)	2013	Breast cancer	[64]
	Brentuximab vedotin	*Approved*		
	Adcetris®	2011	CD30+ lymphomas	[67]

ALL acute lymphoblastic leukemia, *NSCLC* non-small cell lung cancer

action. The use of cationic liposomes that interact with negatively charged endothelial cells of neovasculature could be an option to promote drug uptake into the tumors [30, 32]. Other strategies to improve drug delivery have been explored, such as enhancement of cellular penetration by using fusogenic lipids or other membrane components that ensure the fusion of liposomal membrane with the cellular plasma membrane [20]. Another possibility is to take advantage of receptor-mediated endocytosis that combines selectivity, better drug internalization, and overcoming drug resistance. The development of ligand-targeted liposomes has expanded rapidly, firstly producing immunoliposomes with monoclonal antibodies or antibody fragments attached to the surface of liposomes. To date, patient-applied immunoliposomes are poorly documented and are confined to phase I trials such as, for example, anti-epithelial growth factor receptor (EGFR) doxorubicin immunoliposomes that use antigen-binding fragments of cetuximab as ligand [33].

The association of protein antigens with liposomes has also been used in vaccination therapy, with some success for NSCLC [34]. L-BLP25 [Tecemotide; Stimuvax (Oncothyreon/Merck)] is a liposome vaccine composed of a lipopeptide that targets the exposed core peptide of the mucin 1 (MUC1) tumor-associated antigen. MUC1, an abnormally glycosylated glycoprotein overexpressed in epithelial cells of NSCLC and other types of cancer, promotes tumor growth, increased invasiveness, angiogenesis, and tumor cell survival [35, 37]. Furthermore, immunosuppression correlates with high levels of MUC1 in serum of patients with advanced adenocarcinoma, suggesting a mechanism by which MUC1 overexpressing cells escape strong immune response [35, 36]. The lipopeptide BLP25 specifically targets MUC1, and the insertion of the lipopeptide into the liposome was intended to facilitate uptake by antigen-presenting cells. In this way, the lipopeptide could be delivered into the intracellular space for presentation by MHC molecules [36]. As a result, restoration of the immune cellular response through the induction of antigen T-cell proliferation and production of interferon (IFN)-γ was demonstrated in murine preclinical studies, and later on in clinical trials initiated in advanced NSCLC and prostate cancer [35]. Recent results of a phase III (stimulating targeted antigenic response to non-small-cell lung cancer) trial for stage III NSCLC patients receiving L-BLP25 showed significantly longer median survival (30.8 vs. 20.6 months) in the subgroup of patients treated previously by concurrent chemoradiotherapy [37].

Liposomes responsive either to external stimuli such as heat, ultrasound, or light, or to local triggers such as pH or enzymatic changes is another option to ensure the release of liposomal content inside the tumor [19]. The most clinically advanced liposomal formulation is known under the name of ThermoDox®. These thermosensitive liposomes developed by Celsion release doxorubicin into 41 °C-heated tumors. Thermodox has progressed in clinical trials and, in combination with radiofrequency ablation, is now in phase III for the treatment of hepatocellular carcinoma [38].

4.2 Synthetic Polymer Therapeutics

Ten years ago, Professor Ruth Duncan introduced the definition of 'Polymer Therapeutics' as a new class of polymer-based nanopharmaceuticals that included polymeric drugs (polymers with inherent activity), polymer–drug conjugates, polymer–protein conjugates, polymeric micelles to which the drug is covalently bound, and polyplexes designed as nonviral vectors for gene delivery. These new chemical entities are composed of hydrophilic polymers with versatile chemical synthesis that allow complex or defined architecture for improved drug delivery. Conjugation with PEG by placing a linker between the active protein and the PEG motif was the first strategy to improve the pharmacokinetics and reduce the immunotoxicity of proteins. This technology has then been applied to small molecules such as irinotecan, docetaxel, paclitaxel, or camptothecin [38]. Subsequently, nonbiodegradable polymers such as *N*-(2-hydroxypropyl)methacrylamide (HPMA) became attractive due to their small size (5–100 nm), which enables their elimination by renal or hepatobiliary excretion [40, 41].

Ideally, the nanosized conjugates passively accumulate in tumors by EPR effect then, after endocytosis, the drug is released inside the cell when the linker is degraded by lysosomal enzymes. The potential of these structures is

factual, as illustrated by the growing number of copolymers, biodegradable or not, in industrial pipelines. Currently, 20 polymer–drug conjugates are being evaluated in clinical trials [7].

The most advanced polymer–drug conjugates are NKTR-102 [Etirinotecan pegol (Nektar)] and PPX [CT-210 (CTI BioPharma)] [7]. NKTR-102 is a long-acting PEG conjugate of irinotecan, a topoisomerase 1 inhibitor. The drug, covalently bound to a four-arm PEG, showed an almost four times longer plasma half-life in mice [39]. Evaluated in MBC (phase II), NKTR-102 showed a pharmacokinetic and tolerability profile meeting standards required to further enter a phase III study [42]. PPX is a macromolecular taxane composed of a biodegradable polymer, poly-l-glutamic acid [43]. The release of paclitaxel from the polymeric backbone depends on the activity of lysosomal enzymes, notably cathepsin B, which is overexpressed in many cancers and correlates with tumor invasion. When entered into a phase III trial for NSCLC, PPX yielded similar survival to docetaxel, with less febrile neutropenia and alopecia. A higher incidence of neuropathy was noticed but should be reduced by lowering the starting doses of PPX [44]. Furthermore, preclinical studies showed that PPX produced a stronger radiation enhancement (factor of 4.0–8.0) than paclitaxel alone (factor of 1.5–2.0) [45]. Based on these results, neoadjuvant phase II chemoradiotherapy with PPX and cisplatin was applied to esophageal cancer patients, with encouraging results [46].

Polymer–protein conjugates are based on the same concept as polymer–drug conjugates, but the anticancer agent is a protein [47]. The first example successfully used in anticancer therapy is Zinostatin stimalamer® [neocarzinostatin; SMANCS (Yamanouchi)], a polymer–protein conjugate based on the poly(styrene-co-maleic acid) polymer acting as a nanocarrier for neocarzinostatin, a DNA-damaging protein. Approved for hepatocellular carcinoma in Japan (Table 2), SMANCS presents longer plasma half-life, decreased bone marrow toxicity, and higher tumor accumulation when compared with the free drug [48]. Another successful application is achieved with Oncaspar® [pegaspargase; SS-PEG (Enzon/Sigma-Tau)], an *Escherichia coli* PEGylated L-asparaginase used in ALL. PEGylation has significantly improved L-asparaginase treatment by reducing hypersensitivity reactions and the frequency of administration from several times a week to once every 2 weeks [49]. More recently, calaspargase pegol (SC-PEG) was engineered with a succinimidyl carbonate linker in place of the succinimidyl succinate that links L-asparaginase to PEG. This modification resulted in a similar but more stable formulation. SC-PEG has similar pharmacokinetic, pharmacodynamic, and toxicity profiles to SS-PEG but achieves a longer period of enzyme activity and asparagines depletion in children with ALL [50].

Under specific concentration and temperature conditions in an aqueous medium, amphiphilic polymers self-assemble into micelle structures composed of a hydrophobic core surrounded by a hydrophilic shell [51]. According to their affinity, drugs can be loaded in different compartments of the micelle but, as a result of poor water solubility, drugs are mostly entrapped in the core of the micelle. Polyesters, polyethers and poly(β-amino esters) are the most developed among hydrophobic polymers, while PEG is commonly used as a hydrophilic polymer [52]. A particular example is a triblock polymer known as Pluronic®, consisting of PEG blocks and poly(propylene oxide) (PPO) units arranged in a PEG-PPO-PEG configuration [53]. The interests of polymeric micelles mainly rely on (1) small size (5–100 nm) that enhances pharmacodynamics; (2) high hydrophobic drug payload; and (3) increased blood half-life compared with free drug [54]. It may be noted that these structures entrap old chemotherapeutic drugs such as cisplatin, but taxoids are far more extensively studied. Indeed, Genexol-PM® (IG-100; Samyang Biopharm) is a Cremophor EL free-taxol formulation that avoids severe toxic effects such as hypersensitivity reactions, hyperlipidemia, and peripheral neuropathy. Approved for the treatment of MBC in South Korea (Table 2), Genexol-PM® is under evaluation (phase II) for advanced NSCLC [55]. To date, 15 clinical trials are ongoing to evaluate various synthetic polymer-based nanocarriers. Paclical® (Oasmia Pharmaceutical), paclitaxel polymeric micelles and Livatag® [Doxorubicin Transdrug® (BioAlliance Pharma)], based on biodegradable nanospheres of polyalkylcyanoacrylate, were designed as orphan drugs for ovarian cancer by the US FDA, and for hepatocellular carcinoma by the EU then the FDA, respectively. Paclitaxel polymeric micelles and Doxorubicin Transdrug are currently in phase III study [7, 56].

4.3 Natural Polymers

Human serum albumin (HSA) has emerged in the clinic as a major player in the field of natural nanovectorization. Within two binding sites for exogenous ligands, in addition to those for endogenous ligands, metal ions, and metal complexes, HSA can be loaded with various agents for delivery to their required location. The first example has been the synthesis of ^{99}mTc-aggregated albumin used as a γ-emitting radionuclide imaging agent for the detection of primary cancers and metastases in nuclear medicine [57].

Albumin-based drug conjugates could take advantage of the special mode of albumin transport that facilitates drug accumulation in tumors. It is likely that, taken up by endothelial cells through the interaction of albumin with the 60 kd glycoprotein receptor, the complex drug–albumin, similarly to albumin alone, follows the gp60-mediated

transcytosis pathway through the tumor endothelium. Released into the subendothelial space, albumin–drug conjugates are supposedly sequestered by the albumin-binding protein SPARC (Secreted Protein, Acidic and Rich in Cysteine), resulting in their accumulation into the extracellular space.

In oncology, albumin-bound nanoparticles, known as 'nabs', have been first developed to achieve the following benefit: reduced serious and dose-limiting toxicities of solvent-based formulations by the association of the drug with human albumin [58]. An albumin–paclitaxel conjugate, marketed under the name Abraxane® [ABI-007 (Abraxis/Celgene)], was initially approved in 2005 in the US, and later in 42 countries, for the treatment of MBC. Nab-paclitaxel that avoids the use of cremophor is generally well tolerated, even though cases of persistent polyneuropathy on nab-paclitaxel have been reported. Greater efficiency of nab-paclitaxel was also demonstrated and was further confirmed when compared with Taxotere®, a polysorbate-based docetaxel [59]. Evaluation of nab-paclitaxel, often in combination with conventional chemotherapy, has been extended to other tumors, including NSCLC, pancreatic cancer, melanoma, and head and neck cancer [57]. Because SPARC is closely related to nab-paclitaxel accumulation inside the tumor, its status was considered as a potential predictive biomarker of treatment efficacy. For example, human epidermal growth factor receptor 2+ (HER2+) xenografted tumors with a high level of SPARC expression were found to be more sensitive to nab-paclitaxel than HER2+ tumors with low levels of SPARC [60]. At the same time, higher SPARC expression was correlated with better outcome in patients treated with nab-paclitaxel for either metastatic pancreatic cancer [57] or head and neck cancers [61]. However, the role of SPARC in concentrating intratumor nab-paclitaxel was recently contested. By using a SPARC-deficient, genetically-engineered mouse model of pancreatic ductal adenocarcinoma, it was shown that circulating SPARC is most likely to interact with mouse-nab-paclitaxel to produce drug retention in plasma. Since reduced toxicity of nab-paclitaxel enables a higher than fourfold plasmatic concentration of paclitaxel compared with cremophor formulation, it was suggested that greater nab-paclitaxel efficacy in patients could mainly result from an increased maximum tolerated dose of nab-paclitaxel. In this case, plasmatic levels of SPARC, rather than its intratumor expression, would be predictive for nab-paclitaxel-based chemotherapy [62]. Drugs such as docetaxel, rapamycin [mammalian target of rapamycin (mTOR) inhibitor], 17AAG (HSP90 inhibitor) and INNO-206 (a prodrug of doxorubicin) are other examples of albumin conjugates selected for phase I or II clinical trials (reviewed by Elsadek and Kratz [57]). Apart from albumin, other natural polymers belonging to the glycan family, such as cyclodextrin- or chitosan-based nanoparticles, are under investigation [7].

4.4 Inorganic Nanoparticles

Inorganic nanoparticles carve out a place essentially in tumor imaging and radiosensitization. Intratumor thermotherapy using magnetic nanoparticles is a new approach to increase cytotoxic effects of ionizing radiation. The treatment was applied in patients with recurrent glioblastoma, and consisted of an injection of biocompatible iron-oxide nanoparticles directly into the tumor, then heated by an alternating magnetic field. The treatment combined with reduced radiation dose was well tolerated and achieved longer overall survival in relapsed patients. NanoTherm®, iron oxide nanoparticles developed by Magforce Nanotechnologies, was approved in Europe in 2010 for the thermal ablation of glioblastoma [63].

4.5 Antibody–Drug Conjugates

ADCs constitute a therapeutic modality that corresponds most closely to the definition of 'magic bullet' given by Paul Ehrlich over 100 years ago. Indeed, by combining a drug chemically linked to an antibody, ADCs are designed to achieve both effective targeting and specific drug release into the tumor cells. For this purpose, the three key elements of ADCs (antibody, linker, drug) must comply with the following requirements.

1. Immunogenicity and binding efficiency. Reduced immunogenicity can be achieved by the use of humanized or fully human Ab fragments, while binding efficiency dependent on tumor antigens must be strongly expressed at the tumor cell surface, offering a high affinity of binding. Upon binding of ADCs, ADC internalization through receptor-mediated endocytosis must be realized.
2. Stability of the linker to avoid drug release in circulating blood. Following endocytosis of ADCs, the linker must be cleavable in lysosomes at low pH or protease activity to ensure drug release inside the tumor cell.
3. ADC should be efficient at low, subnanomolar drug concentrations. This is related to the low percentage of antibody that reaches the tumor (0.003–0.08 % injected drug per gram of tumor). Two classes of drugs meet these requirements: microtubule inhibitors and DNA-damaging agents [64, 65].

It is not easy to combine all these elements together and despite adequate antibodies such as the anti-CD20 monoclonal antibody rituximab or anti-HER2 antibody

trastuzumab (Herceptin®), few ADCs have been approved to date for clinical use. The most promising ADC in the treatment of solid tumors is probably trastuzumab–emtansine (T-DM1), which combines trastuzumab with mertansine (DM1), a maytansinoid known to be a potent tubulin polymerization inhibitor. Hence, T-DM1 takes advantage of the anti-HER2 properties of trastuzumab and by disrupting microtubule networks in the cell, T-DM1 produces cell-cycle arrest and apoptotic cell death [65]. Under the name Kadcyla® [ado-trastuzumab emtansine (Roche/Genentech, ImmunoGen)], T-DM1 was approved by the FDA in February 2013 for use as a single drug in the treatment of patients with HER2+ MBC who previously received trastuzumab and a taxane separately or in combination [66]. Ongoing developments of T-DM1 in patients with early-stage HER2+ breast or gastric cancer (phase II/III) are expected to confirm both antitumor activity against HER2+ tumors and favorable tolerability when compared with reference treatments [66, 67]. Evidence already suggests that patients with higher levels of tumor HER2 messenger RNA (mRNA) are more likely to benefit from trastuzumab-based treatment [67].

In hematological malignancies, the first approval of the therapeutic monoclonal antibody Orthoclone (OKT3®) in 1992 offered the possibility of developing antibody-based therapeutic strategies that would become effective in clinical practice. In 2000, the FDA approved the ADC gemtuzumab ozogamicin [Mylotarg® (Pfizer/Wyeth)], composed of anti-CD33 monoclonal antibody linked to a modified calicheamicin, for the treatment of CD33+ patients with acute myeloid leukemia. Ten years later, gemtuzumab ozogamicin was withdrawn from the US market after no apparent clinical benefit. However, the administration of fractionated doses of gemtuzumab ozogamicin which allow the safe delivery of higher cumulative doses was recently shown to improve efficacy while reducing toxicity [68]. Currently, two ADCs have reached phase III development; one of these, Brentuximab vedotin [SGN-35; Adcetris® (Seattle Genetics)], received accelerated FDA approval in 2011 in case of refractory or relapsed Hodgkin lymphoma (HL) and systemic anaplastic large-cell lymphoma (ALCL). Brentuximab vedotin is composed of a chimeric anti-CD30 monoclonal antibody linked to an auristatin derivative, a potent inhibitor of tubulin polymerization. It may be noted that unconjugated CD30 antibodies failed in the treatment of HL or ALCL, although CD30, a transmembrane glycoprotein from the tumor necrosis factor receptor family, is consistently overexpressed in both hematologic malignancies [69].

On the border line of nanotherapeutics, monoclonal antibodies labeled with a radionuclide belong to the family of radioimmunotherapeutics. Zevalin® [ibritumomab tiuxetan (IDEC Spectrum)] and Bexxar® [tositumomab (Corixa GlaxoSmithKline)] were approved by the FDA for the therapy of non-HL, but tositumomab was withdrawn in 2014 [70].

5 Conclusions

The era of nanomedicine is still in its infancy, even though nanotechnology has already provided many concepts that could be applied in oncology. Research institutes contribute significantly to their engineering, but beyond the design and development of increasingly complex nano-sized drug formulations, the pharmaceutical industry is faced with difficulties in large-scale production. Quality controls and production costs of such sophisticated nanoparticles are probably a hindrance to their clinical transfer [71]. The toxicity of nanoparticles for human health and the environment is another key issue. Acute and chronic toxicities are the subject of specialized studies, and an increasing amount of data can now be taken into account to improve the engineering of future nanotherapeutics [7, 72]. Taken as a whole, extensive preclinical knowledge and clinical expertise is being accumulated and it is quite likely that nanomedicines will rapidly emerge in the diagnostic and therapeutic arsenal in oncology.

Compliance with Ethical Standards

Conflicts of interest Sophie Marchal, Amélie El Hor, Marie Millard, Véronique Gillon and Lina Bezdetnaya attest no conflicts of interest.

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