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A review on engineering polymer drug conjugates to improve combination chemotherapy

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ABSTRACT

Combination chemotherapy treatments with polymer drug conjugates (PDCs) have been designed to overcome the limitations of traditional chemotherapy. While there are many significant design challenges associated with engineering a combination therapy with PDCs, several studies have shown therapeutic benefits of incorporating multiple drugs onto a polymeric carrier. Here, we summarize the chemistries and biological performance of different combination PDCs that have been tested in the preclinical setting and offer recommendations for future studies which will provide the necessary information to streamline future translation.

1. Introduction

Cancer remains the second leading cause of death in the United States, following cardiovascular disease [1]. Due to the development of single drug resistance and dose-limiting toxicities with traditional chemotherapy and tumor heterogeneity, combination chemotherapy is commonly used in the clinic to treat many late-stage cancer subtypes [2–6]. While patients' tumors often respond to combination chemotherapy, overall efficacy is limited due to increased toxicity [7].

In an attempt to increase the overall efficacy and reduce toxicity, drug delivery systems (DDS) carrying various combinations of chemotherapeutic agents have been engineered and tested [8•,9]. Such systems can improve the bioavailability of chemotherapeutics, and deliver precise ratios of the agents directly to the cancer site. Liposomes, polymeric nanoparticles, inorganic nanoparticles, polymeric micelles, and polymer drug conjugates (PDCs) designed to carry combinations of chemotherapy agents have shown better efficacy in preclinical models compared to free drug combinations. Furthermore, VYXEOS™ (CPX-351), a liposomal formulation carrying daunorubicin and cytarabine, significantly extended patient survival over the standard care in a phase III clinical trial while treating secondary acute myeloid leukemia (AML).

Of all systems engineered thus far to deliver chemotherapy agents, PDCs are unique and offer multiple advantages. Instead of physical encapsulation, drugs are chemically conjugated to a polymer, and the drug ratio and subsequent release rates are governed by the chemistry used to incorporate the drugs. While few combination PDCs have entered the clinic, the activity of single agent PDCs in clinical trials, most notably the ability to decrease toxicity, give rise to further motivation in continuing the development of PDC-based combination chemotherapy [10–15].

As discussed in a 2009 review [16•], designing an effective combination chemotherapy with PDCs is a significant challenge due to the large design space involving chemistry, biology, and materials science. Here, we briefly summarize the polymers and chemistries that have been used to incorporate single agents and briefly discuss recent clinical translation. We then thoroughly review the various types of combination PDCs that have been tested recently both *in vitro* and *in vivo* and evaluate their biological performance based upon physiochemical properties. Lastly, we offer recommendations on future combination PDC development, with an emphasis on clinical translation.

2. Polymers in PDCs

Macromolecular-based drug carriers have evolved continuously since Ehrlich proposed the idea of a “magic bullet” in 1906. The development of polymeric carriers for non-cancer drugs [17–20] laid the foundation for Helmut Ringsdorf's clear model for delivering drugs using pharmacologically active polymers in 1975 [21]. Since then, a variety of PDC systems have been engineered to deliver chemotherapeutic agents and have been studied extensively *in vivo* [22–27].

PDCs offer many advantages to traditional chemotherapy by manipulating the properties of the drug. For example, conjugating a small molecule drug to a polymer can improve the drug's solubility in water, protect it from systemic degradation, and increase drug circulation time. In addition, macromolecular carriers with extended

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circulation can accumulate in tumors with irregular vasculature through the enhanced permeability and retention ("EPR") effect [28–30]; however, this is not applicable to all tumors [31,32]. While each polymer-drug system has its own physical characteristics, a few general trends have been observed in the field. For example, studies have shown that polymers with a higher molecular weight tend to circulate longer in the plasma due to reduced renal clearance rates, and can accumulate higher at the tumor [33,34]. Furthermore, there are multiple structural factors which impact conjugate performance including polymer architecture and chemical linkers, which is summarized in the following review [35].

With the goal of reducing systemic toxicity while still achieving tumor regression, a wide range of natural and synthetic water-soluble polymers have been evaluated in the first generation of polymer therapeutics and its subsequent clinical testing. Here, we will briefly discuss the polymers used in these conjugates, with an emphasis on the advantages of each polymer platform. A summary of the PDCs tested in the clinic can be found in Table 1.

2.1. HPMA copolymer-drug conjugates

Although a synthetic polymer, *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer is the most versatile and greatly explored polymer used in PDCs. HPMA is highly soluble in water, nontoxic, non-immunogenic, and capable of circulating in the blood for extended periods due to non-adsorption of plasma proteins [36]. HPMA copolymer synthesis has evolved from the free radical polymerization of *co*-monomers of HPMA and methacrylated (MA)-peptidyl-nitrophenylester (ONp) to the polymerization of derivatives of drugs, such as (MA)-peptidyl-drug [36,37••,38]. Although non-biodegradable, HPMA-drug conjugates with a molecular weight (MW) <40 kDA can be eliminated from the body *via* renal filtration. Further, multi-block degradable HPMA conjugates have been designed to allow for larger constructs to be administered systemically and still be cleared [39].

Various HPMA products have been evaluated in clinical trials, including conjugates carrying doxorubicin (DOX), paclitaxel (PTX), camptothecin (CPT), and dichloro(1,2-diaminocyclohexane)platinum(II) (DACHPt, the oxaliplatin parent complex) [13,15,40,41]. In all of the trials, 20 to 30 kDa HPMA copolymers were used with the peptide cleavable linker GFLG or acid labile linkers. In addition, a targeting ligand was also evaluated by conjugating both galactosamine and DOX to HPMA (PK2) [42]. The majority of the phase I and II clinical trials reported acceptable toxicity with partial responses during treatment of various cancers. All conjugates reported improved drug bioavailability and tolerable toxicity profiles, and the conjugate carrying DACHPt (ProLindac) has shown promising clinical results. Phase I/II clinical evaluation of ProLindac in patients with recurrent ovarian cancer demonstrated an excellent safety profile and antitumor efficacy. Subsequently, a multicenter-based evaluation of ProLindac in combination with Paclitaxel (PTX) is being pursued in Europe for treatment of late stage ovarian cancer [43].

2.2. Polysaccharide–drug conjugates

Polysaccharide-based systems are highly attractive due to their biocompatibility, biodegradability, and synthesis costs. Polysaccharides are soluble in water and have various functional groups to conjugate drugs. Due to their ability to be degraded naturally, higher MW conjugates can be administered to enhance plasma retention times. In addition, certain polysaccharides are capable of specifically binding to cancer cells, such as hyaluronic acid (HA) which binds to CD44 (a cell surface receptor that is highly expressed on cancer cells).

Polysaccharide-drug conjugates that have entered clinical trials were primarily based upon hyaluronic acid (HA), dextran (DEX), and cyclodextrin. Many of these conjugates, including AD-70 (oxDEX-DOX), DE-310 (cmDEX-exatecan), and MEN 4901/T-0128 (cmDEX-T-2513) showed excellent response rates, but severe toxicity limited the treatments [44–46]. A paclitaxel conjugate with HA administered with intravesical therapy showed excellent efficacy while treating bladder cancer locally [47]. In addition, a β-cyclodextrin-PEG copolymer with CPT (CRLX-101) is currently being evaluated for treating various types of cancers in phase 2 trials due to promising phase 1 results [12].

2.3. PEG-drug conjugates

Poly (ethylene glycol) (PEG) is a commercial polymer widely used in FDA-approved biological applications. Due to its hydrophilic nature and

Table 1
Summary of single drug PDCs evaluated in the clinic.

Conjugate name	Polymer-drug	MW (kDa)	Clinical trials (cancer, phase)
HPMA-drug conjugates			
PK1 [11,13]	HPMA-DOX	30	Non-small cell lung, breast cancers (Phase II)
PK2 [42]	HPMA-DOX-galactosamine	25	Hepatocellular carcinoma (Phase I/II)
PNU-166945 [40]	HPMA-PTX	25	Refractory solid tumors (Phase I)
PNU-166148 [41]	HPMA-CPT	18	Gastric and gastroesophageal tumors (Phase I)
AP-5346 [15]	HPMA-DACHPt	25	Ovarian cancer (Phase I/II)
Polysaccharide-drug conjugates			
ONCOFID-P-B [47]	HA-PTX	200	Bladder carcinoma refractory to BCG (Phase I)
AD-70 [44]	oxDEX-DOX	70	Various advanced cancers (Phase I)
DE-310 [45]	cmDEX-exatecan	360	Metastatic adenocarcinoma (Phase I)
MEN 4901/T-0128 [46]	cmDEX-T-2513	130	Solid tumors (Phase I)
CRLX101, IT-101 [12]	β-Cyclodextrin-PEG-CPT	57	Advanced tumors (Phase I)
PEG-drug conjugates			
PROTHECAN [49]	PEG-CPT	40	Advanced solid malignancies (Phase I)
EZN-2208 [50]	PEG-SN38	40	Metastatic colorectal and breast cancers and pediatric cancer (Phase II)
NKTR-102 [51]	PEG-Irinotecan	20	Ovarian, breast, colorectal, and cervical (Phase II)
NK911 [52]	PEG-b-PASA-DOX	16	Metastatic pancreatic cancer (Phase II)
NC-6300 [53]	PEG-b-PASA-EPI	20	Advanced or metastatic solid tumors (Phase I)
NK012 [54]	PEG-b-PG-SN38	19	Small cell lung cancer (Phase II)
NC-6004 [10]	PEG-b-PG-CIS	26	Locally advanced or metastatic pancreatic cancer (Phase III)
NC-4016 [55]	PEG-b-PG-DACHPt	18	Advanced solid tumors or lymphoma (Phase I)
PG-drug conjugates			
XYOTAX, CT-2103 [56,58]	PG-PTX	39	Non-small cell lung cancer (Phase III)
CT-2106 [57]	PG-CPT	49	Advanced solid malignancies (Phase I)