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Development of HPMA copolymer–anticancer conjugates: Clinical experience and lessons learnt☆

Ruth Duncan *

School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, UK

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ABSTRACT

The concept of polymer–drug conjugates was proposed more than 30 years ago, and an *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer conjugate of doxorubicin covalently bound to the polymer backbone by a Gly-Phe-Leu-Gly peptidyl linker (FCE28068) became the first synthetic polymer-based anticancer conjugate to enter clinical trial in 1994. This conjugate arose from rational design attempting to capitalise on passive tumour targeting by the enhanced permeability and retention effect and, at the cellular level, lysosomotropic drug delivery to improve therapeutic index. Early clinical results were promising, confirming activity in chemotherapy refractory patients and the safety of HPMA as a new polymer platform. Subsequent Phase I/II trials have investigated an HPMA copolymer-based conjugate containing a doxorubicin and additionally galactose as a targeting moiety to promote liver targeting (FCE28069), and also HPMA copolymer conjugates of paclitaxel (PNU 166945), camptothecin (PNU 166148) and two platinates (AP5280 and AP5346- ProLindac™). The preclinical and clinical observations made in these, and clinical studies with other polymer conjugates, should shape the development of next generation anticancer polymer therapeutics.

Contents

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* Tel.: +44 2920916160.
E-mail address: duncanr@cf.ac.uk.

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1. Introduction

1.1. General background

Although Helmut Ringsdorf first proposed the concept of polymer–anticancer drug conjugates in 1975 [1] most early systems rarely progressed beyond *in vitro* testing. Lack of a sound biological rationale meant that most conjugates tested *in vivo* were ineffective. For this reason, and also uncertainly of the value of polymers as carriers per se (antibodies and proteins were much more favoured as a more 'biologically' acceptable platform), the community was slow to embrace the value of this approach. Polymer–drug conjugates were viewed as "nice science" but an impractical mix of polymer and organic chemistry resulting in compounds so complicated that they would never be developed clinically. These conceptual reservations were compounded by the fact that polymers used pharmaceutically have many different well-known forms including implants, gels, and excipients (often as tablets and capsules). Historically, and still today, this leads to confusion. Moreover, the use of water-soluble polymers as solutions for injection was then much less appreciated. Over the last 20 years oncologists have become increasingly familiar with 'polymers' in their many guises. Biodegradable polymeric implants are routinely used both as a subcutaneous (s.c.) depot to slowly release LHRH analogues (e.g. Zoladex®; Leupron Depot®) [2], for treatment of prostate and other hormone-dependent cancers, and for implantation post-gliobastoma surgery to local delivery chemotherapy for treatment of residual or recurrent disease (e.g. Gliadel®) [3]. Moreover, over the last 15 years there have been a growing number of polymer conjugates, especially PEG-proteins that have come to market (reviewed elsewhere in this issue), and polymeric micelles entering clinical trials as anticancer agents and also, for micelles, as non-covalent drug delivery systems (reviewed in [4]).

Early studies focused on both natural and synthetic polymers. Still a popular question today — which is best? The appropriate answer is neither. In this field it is essential to choose the correct polymer for each specific application/route of administration. Earlier on, polysaccharides were widely explored, dextran being particularly popular owing to its clinical approval for use as a plasma expander. A dextran–doxorubicin conjugate (AD-70) was the first polymer–drug conjugate to be tested clinically, the clinical formulation being supplied by Alpha Therapeutic GmbH. Anthracycline conjugation seemed by Schiff base formation to oxidised dextran also modified with glycine as a pendant group [5]. The rationale was to utilise tumour hypoxia to promote drug liberation. However, in a Phase I trial (13 patients) when AD-70 was administered every 21–28 days by a 30 min infusion unexpected toxicities (severe thrombocytopenia and hepatotoxicity) occurred, even at the starting dose of 40 mg/m^2 (doxorubicin-equivalent) [5]. To note this is approximately half the recommended dose for doxorubicin (also known as Adriamycin®), which used clinically at a dose of 60–75 mg/m^2. Despite dose reduction to 12.5 mg/m^2 toxicity was still seen. AD-70 induced hepatotoxicity lasting for several weeks suggesting liver localisation with slow release of doxorubicin thereafter. This toxicity was attributed to reticuloendothelial (RE) cell uptake of the poly(glucose) and/or the fact that doxorubicin was conjugated to oxidised dextran so residual aldehyde groups would likely be present after drug conjugation. Phase II studies were neither reported for this compound nor a carboxymethyldextran–camptothecin conjugate (DE-310) that comprised a camptothecin analogue DX-8951f was covalently bound to the carbohydrate carrier via a Gly-Gly-Phe-Gly peptide linker [6]. Our research in the 1980s (supported by the Cancer Research Campaign (CRC UK) and Farmitalia Carlo Erba (became Pharmacia now Pfizer) in collaboration with the Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic Prague) designed the first two synthetic polymer–drug conjugates to enter clinical trial as anticancer agents for intravenous (i.v.) injection. These were based on *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymers. This history has been well documented although mostly from an academic viewpoint [7–13]. Here the rationale for design of lead compounds, key steps in preclinical development and the current clinical status of HPMA copolymer-based anticancer agents is reviewed. The challenges for effective clinical development of these complex macromolecular prodrugs are also discussed.

All polymer–anticancer drug conjugates progressing through clinical trials as anticancer agents are in effect macromolecular prodrugs. They typically comprise a minimum of three components; a natural, synthetic or pseudosynthetic (e.g. poly(glutamic acid); PGA) water-soluble polymeric carrier usually of molecular weight 10,000–100,000 g/mol; a biodegradable polymer-drug linkage, and the bioactive antitumour agent (reviewed in [4,7,11]). It should be noted that many of the drugs so far attached (e.g. anthracyclines, taxanes, and camptothecins) were chosen in the 1980s and 1990s when these molecules were first introduced into routine clinical practice. There are now many more modern and interesting candidates. Most of these pendant drugs are extremely hydrophobic causing the conjugate to adopt a nanosized, unimolecular micelle conformation in aqueous solution (typically 5–20 nm) [14]. As new chemical entities (NCEs) these conjugates have been rightly defined as polymer therapeutics rather than (non-covalent) drug delivery systems such as liposomes and nanoparticles that simply entrap drugs (reviewed in [4,15]). They also fall within the definition of "nanomedicines or nanopharmaceuticals" adopted by the European Science Foundation's Forward Look on Nanomedicine (reviewed in [16]). In certain cases ligands have also been introduced with the hope of promoting receptor-mediated tumour targeting. For example, the HPMA copolymer–doxorubicin conjugate that contains additionally galactosamine (FCE28069) designed in the early 1980s [17] to target the hepatocyte asialoglycoprotein receptor was the first synthetic, multivalent natural mimetic conjugate to enter clinical testing. To aid preclinical pharmacokinetic studies and facilitate clinical imaging, imaging agents have also been incorporated into the conjugate. This, together with the recent move towards conjugates carrying combination therapy often results in highly complex, multifunctional, structures (Fig. 1). To note that schematic representations that show polymer conjugates as a "washing line" (see cartoon of Ringsdorf [1]) are outdated and indeed unhelpful. It has clearly been shown that many polymer conjugates form a unimolecular micelle in aqueous solution. The 'compactness' and structure of these dynamic structures (expected to change as pendant moieties are liberated) has a significant effect of biological properties such as enzyme access, targeting ligand–receptor interaction and will also influence pharmacokinetic properties. There is an urgent need to define and better understand the structure–activity relationships of these complex architectures.