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ORIGINAL ARTICLE

Macromolecular Drugs: Novel Strategy In Target Specific Drug Delivery

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ABSTRACT

Macromolecular drugs are polymer-conjugated drugs, polymeric micelles, liposomal drugs or solid phase depot formulations of various agents. Macromolecular drugs can target selectively, solid tumours by exploiting abnormalities of tumour vasculature, namely, hypervascularisation; aberrant vascular architecture; extensive production of vascular permeability factors stimulating extravasation within tumour tissues; and lack of lymphatic drainage. Dextrans are polysaccharide macromolecular carriers devoid of selective transport properties and may serve as one of the most promising carrier candidates for a wide variety of therapeutic agents like hormones (oxytocin and vasopressin), iron, methotraxate, etc. Bone targeting by conjugation of drugs with bisphosphates has shown promise in enhancing their effects in bones and reducing adverse drug reactions. Tetracyclin–conjugated estradiol and oligopeptide–conjugated estradiol are the other novel bone–specific drug carriers (oligopeptides) with high affinity for hydroxyapatite crystals.

Key Words: polymer-conjugated drugs, Dextrans, Tetracyclin–conjugated estradiol, bisphosphates.

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Introduction

Macromolecular drugs are polymer-conjugated drugs, polymeric micelles, liposomal drugs or solid phase depot formulations of various agents[1]. Candidate polymers for therapeutic use must be devoid of antigenicity, immounogenicity, haemolytic, procoagulant or cytotoxic activity. Macromolecular drugs must be neutral or slightly negatively charged, as the luminal surfaces of the blood vessels are negatively charged[1]. Polymeric drugs can be made through covalent linking of drugs to a polymeric carrier; whereas micellar entrapment of a drug can be achieved by covalent or noncovalent bonds. Amide, ester, hydrazide, azide, imine, thioether, urethane etc. are various chemical bonds used to prepare macromolecular drugs. Polymeric drugs have the advantage of having long t ½ activity against MDR (multidrug resistant) cells, and high retention in the tumour cells.[1]Drugs weighing less than 40 kDa, unless bound to plasma protein, are cleared rapidly into urine, whereas drugs weighing more than 40 kDa usually have long t ½. However, accumulations of drugs should be kept in mind if used for long durations. Moreover, drugs > 40 KDa are taken inside the cell by endocytosis, transported to lysosomes and the active component is released by proteolytic enzymes at low pH.[1] Thereby, these macromolecules counteract the P-glycoprotein-dependent efflux system in MDR. Newly formed tumour vessels are abnormal in form and architecture of fluid transport dynamics (especially tumour tissues lack effective lymphatic drainage), which results in enhanced permeability and retentions of macromolecules and lipids in the tumour cells.

Macromolecules As Anticancer Drugs

[2],[3]Lack of tumour selectivity is the major limitation inherent to most conventional anticancer chemotherapeutic agents. Macromolecular drugs can target solid tumours selectively by exploiting abnormalities of tumour vasculature, namely, hypervascularisation; aberrant vascular

architecture; extensive production of vascular permeability factors stimulating extravasation within tumour tissues; and lack of lymphatic drainage. Large molecular size, nanosized macromolecular anticancer drugs administered intravenously, escape renal clearance, cannot penetrate the tight endothelial junctions of normal blood vessels, and can extravasate in tumour vasculature and become trapped in the tumour vicinity. Due to lack of efficient lymphatic drainage in solid tumours, there will be a severalfold increased concencentration of the drug in the tumour, than in the plasma. EPR (enhanced permeability and retention effect) - based selective anticancer drug delivery has hastened the development of various polymer conjugates and polymeric micelles, as well as multifunctional nanoparticles for targeted cancer chemotherapy. Increased efficiency of drug delivery to the tumour, especially of macromolecular drugs, is possible by enhancing the EPR effect with the use of various vascular permeability mediators or potentiators. Suppression of the EPR effect by the use of appropriate inhibitors like bradykinin antagonist HOE 140, protease inhibitors, or NOS inhibitors, may also be possible. Pleural fluid in lung cancer and ascitic fluid in abdominal carcinomatosis may be controlled, and the clinical course of cancer patients may be improved by suppressing vascular permeability with antidotes such as the bradykinin antagonist HOE 140.

Some of the macromolecules showing promises in clinical therapeutics are as follows:

Styrene Maleic Acid Neocarzinostatin

[1] It is a proteinaceous antitumour antibiotic produced by streptomyces carzinostaticus. It acts by inhibiting DNA synthesis through direct DNA strand scission and superoxide generation via a cytochrome p450 reductase .It has prolonged t ½ (10-20 times more than that of neocarzinostatin), with high targeting efficiency. It gets split into neocarzino statin and styrene maleic acid (SMA) polymer by proteolysis, and free MA polymer is eliminated (more through bile and less through kidney). Its efficacy against primary hepatocellular carcinoma and solid tumour has been reported after intra-arterial administration. It shows a 10-28 times higher binding affinity to tumour cells than neocarzinostatin, and can be given orally. Moreover, it has reduced immunogenicity and high plasma albumin binding capacity.

Peginterferon Alfa

[1] Interferon α, β and γ are used as antitumour agents in renal cell cancer, kaposi's sarcoma or leukaemia, and for management of HCV(hepatitis c virus).Being smaller in size, they have short plasma t ½ (8hrs.). Pegylated (PEGylation is the process of covalent attachment of poly(ethylene glycol) polymer chains to another molecule versions) of IFN α-2a and IFN α -2b are developed with prototypes having single straight chain polyethylene glycol (PEG) molecules of 5 KDa and 12 KDa per molecule of interferon, respectively. Further improvement is made by conjugating IFN - α-2a with the 40 KDa PEG moiety. The PEG-IFN-α-2a (subcutaneous) produces slower penetration and delivery to the circulating blood and has decreased systemic clearance to $1/10^{th}$ of the native protein. 2',5' oligoadenylate synthetase, an antiviral response enzyme reaches its maximum level at 48 hr. and remains at a plateau for over 1 week after PEG-IFN α-2a administrations, as compared to the maximum level at 24 hrs after IFN α-2a administration. Moreover, PEG IFN α -2a (40 KDa) has better tolerability profile than IFN α-2a, and is associated with better safety profile than IFN α -2a + ribavirin therapy (anaemia associate with rebavirin therapy), with better out come in HCV infection .

Pegylated Liposomal Doxorubicin

[1] Liposomes are coated with PEG to confer a stealth character, resulting in a diminished uptake by the reticuloendothelial system, and hence a longer plasma t ½ . FDA has already approved pegylated liposomal doxorubicin for treatment of AIDS related kaposi's sarcoma. In a phase II study, it has been shown that mesothelioma pegylated liposomal doxorubicin is effective, with modest toxicity. PEG-immunoliposome encapsulated doxorubicin (MCC-465), where PEG is tagged with the $F(ab)_2$ fragment of human antibody IgG against gastric caranoma, is currently under clinical investigation for treatment of stomach cancer.

Pegylated Adenosine Deaminase

[1]PEGF-conjugatedADA(adenosine deaminase), has a human t ½ of 48-72 hours, and its once weekly administration in a dose of

15 U/kg significantly reduces adenosine levels in erythrocytes and results in full restoration of lymphocyte function .PEG-conjugated ADA was approved by US FDA in 1990 for use in conjugated adenosine deaminase deficiency.

Pegaspargase

[1] Severe allergic reactions and pancreatitis are reported with use of L-aspargine from E. Coli and plant pathogen Erwinia. Conjugation of PEG to E coli L-asparaginase results in reduction in toxicity and prolonged plasma t ½.

Dextran conjugates as macromolecular drugs

[4]Dextrans are polysaccharide macromolecular carriers devoid of selective transport properties, and may serve as one of the most promising carrier candidates for a wide variety of therapeutic agents due to their excellent physico-chemical properties and physiological acceptance. Dextrans of different chemical composition are synthesized by a large number of bacteria confined to the family Lactobacillaceae, Streptobacterium dextranicum and Leuconostoc mesenteroids. The product of microbiological synthesis is called as 'native-dextran'. Clinical dextrans are obtained from high molecular weight native dextrans after their partial depolymerisation by acid hydrolysis and fractionation. Dextran conjugates can either be irreversibly linked or reversibly linked. Irreversible dextran conjugates have been employed extensively in experimental medicine, and find wide applications in the field of biotechnology and related areas. Important enzymes that have been linked to dextran are a-amylase, arginase, asparaginase, carboxypeptidase, catalase, β -galactosidase, hyaluronidase, NAD+, streptokinase, papain and a-chymotrypsin. Various hormones like oxytocin and vasopressin have been linked to dextran so as to increase their water solubility along with retention of their activity. Enhanced lymphatic uptake of bleomycin, improved therapeutic efficiency of isometamidium, and reduced nephrotoxicity of gentamicin has been reported, when these drugs were administered in the form of dextran sulphate complexes. Parenteral iron-dextran has been used for the rapid regeneration of the red cell mass in anaemia and in patients intolerant of oral forms of iron. Pentavalent antimonials are rapidly excreted in urine, and have short duration of action. So, it has been complexed with dextran, which after intramuscular injection, is slowly absorbed from the injection site, and hence sufficient blood levels are maintained so as to suppress the Leishmania donavani infection effectively. Dextran can be attached to the drug to form a prodrug by various techniques like direct linkage, attachment through intercalated spacer arm, use of modulator ligand and tissue specific receptor ligand e.g., methotrexate (MTX)-dextran conjugates, Dextran-nalidixic acid ester (colon specific prodrug).

Conjugates of Bisphoshonates

[5]Bisphosphonates are synthetic compounds structurally related to pyrophosphate, an endogenous regulator of calcium homeostasis. Because of the P-C-P portion in its chemical structure, it has high affinity for calcium crystals, high bone specific delivery, and high water solubility with kidney as the major route of elimination. Moreover, unlike the POP bond of pyrophosphate, the PCP bond in bisphosphates is resistant to chemical and enzymatic hydrolysis. Hence, after binding to bone, bisphosphates remain there for a long period, with a t ½ of several months. Bone targeting by conjugation of drugs with bisphosphates has shown promise in enhancing their effects in bones and reducing adverse drug reactions.

Tetracyclin–conjugated estradiol and oligopeptide–conjugated estradiol are the other novel bone–specific drug carriers, which are oligopeptides with a high affinity for hydroxyapatite crystals.[5] Estradiol conjugated with hexa-L-aspartic acid peptide and E_2-(L-ASP) after a once weekly treatment, showed an efficacy similar to estradiol treatment every 3 days, with less side-effects.[5] It has advantage over bisphosphonates conjugates, as no colloid or precipitate formation is there, with endogenous metals. Radiopharmaceuticals beta-emitter ^{153}Sm is coupled to the phosphonate part of EDTMP (ethylenediamine –tetramethyl-lene phosphonic acid) in a 1:1 ratio with high affinity for bone minerals and skeletal muscles, and has high accumulation in metastatic regions (4 times more than normal tissue) .[5] ^{153}Sm is also a gamma emitter, hence having advantages of medical imaging for delineating the progression of bone metastases. Fibroblast growth factor-I, bone morphogenetic proteins and transforming growth factor B are also being investigated as potential agents for bone specific delivery, in

conjugation with bisphosphonates in osteoporosis.

Macromolecular drugs against human immunodeficiency virus Type1(HIV-1)

[6]Macromolecular drugs against human immunodeficiency virus Type 1 (HIV-1), including antisense oligonucleotides, ribozymes, RNA decoys and transdominant mutant proteins, may be able to interfere with a relatively large number of viral targets, thereby decreasing the likelihood of the emergence of drug-resistant strains. Moreover, it is relatively easy to alter the sequence of some of the macromolecular drugs to counter emerging drug-resistant viruses. The delivery of antisense oligonucleotides and ribozymes to HIV-1 infected or potentially infectable cells by antibody-targeted liposomes, certain cationic lipid formulations and pH-sensitive liposomes, result in significant anti-HIV-1 activity. Delivery of therapeutic genes is another form of macromolecular drug. Moloney murine leukaemia virus- (MoMuLV), adeno-associated virus (AAV)-, or HIV-derived vectors expressing a variety of therapeutic genes, have been used successfully to inhibit HIV-1 replication in cultured cells.

Potential targets for production of conjugated molecules are prostaglandin E2, estradiol and synthetic estrogenic agents for osteoprosis, NSAIDS for osteoarthritis, fluoroquinolones for chronic infections and cisplatin, melphalan, methotrexate and radiopharmaceuticals for cancers[5]. Macromolecular drugs may prove to be a novel mode of drug delivery to target site, avoiding side effects with prolonged duration of action and less potential for drug resistance.

References

[1] Greish K, Fang J, Inutsuka T, Nagamitsu A and Maeda H. Macro molecular therapeutics advantages and prospects with special emphasis on solid tumor targeting . Clin Pharmacokinet 2003; 42(13): 1089-105.

[2] Greish K. Enhanced permeability and retention of macromolecular drugs in solid tumors: a royal gate for targeted anticancer nanomedicines. J Drug Target. 2007 Aug-Sep; 15(7-8):457-64.

[3] Fang J, Sawa T, Maeda H. Factors and mechanism of "EPR" effect and the enhanced antitumor effects of macromolecular drugs including SMANCS. Adv Exp Med Biol. 2003; 519:29-49.

[4] Dhaneshwar SS, Kandpal M, Gairola N, Kadam SS. Dextran: A promising macromolecular drug carrier. Indian J Pharm Sci 2006; 68:705-14.

[5] Hirabayashi H and Fujisaki J. Bone specific drug delivery systems: approaches via chemical modification of bone-seeking agents. Clin Pharmacokinet 2003; 42(15): 1319-30.

[6] Konopka K, de Lima MCP, Simões S, Rossi JJ, Düzgünes N. Delivery of novel macromolecular drugs against HIV-1. Expert Opinion on Biological therapy. 2001; 1(6):949-70.