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A MODERN APPROACH IN ANTICANCER THERAPY USING ADEPT: AN OVERVIEW

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ABSTRACT

Anticancer drugs selectivity is improved by strategy called Antibody-directed enzyme prodrug therapy. It is a two-step process which benefits over radioimmunoconjugate, chemo-toxin etc. The main functions of Antibody-directed enzyme prodrug therapy are prodrug activation by enzyme and targets cancer cells by the conjugates and selectivity characteristics of prodrug/drugs/enzymes are reviewed. Generation of cytotoxic agents at tumor sites by antibody vectored enzyme from non-toxic pro-drugs. The traditional approach improves the properties of prodrugs which include solubility, permeability, stability, distribution etc. but this therapy improves selectivity. The activation of prodrugs is mainly governed by enzymes that are at higher amounts in tumors, which leads to selective antitumor activity.

KEYWORDS

ADEPT, Targeting, Enzymes, Prodrug, Antibody-enzyme conjugates and Tumor therapy.

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INTRODUCTON

The main causes of death that account for about 13% of mortality rate is cancer[1]. Traditional cancer treatment includes chemotherapy, radiotherapy and surgery which have drawbacks, as it affects the normal cells in the body and also epithelial and intestinal cells. The aim of ADEPT is to kill the cancerous cells without affecting the normal cells and one of those approach is ADEPT (antibody directed enzyme linked prodrug therapy) which is a two-step process[2,3]. Conventional pro-drugs aim at improving aqueous solubility, stability, absorption and permeability along with reduction in unacceptable taste, pain, irritation, metabolism and

toxicity[4,5]. In order to target specific antigen, enzymes and peptide transporters with over expression on tumor cell than normal cells, prodrugs can be designed, which can be achieved by conjugating tumor-specific ligand to drug by a cleavable linker[6]. The administration of the repeated doses of conjugates may be blocked due to the major disadvantage of the conjugates like immunogenicity. The wide extent of prodrug, antibodies and enzymes has been fashioned for ADEPT and are reviewed[7-13].

MATERIAL

Antibodies

Pro-drug activation for localizing is ensured by antibodies that bind to the tumor associated antigen as a major key factor in ADEPT due to higher affinity and covalent binding. Two major factors that affect the penetration of conjugates mainly are leaky blood vessels and interstitium of tumorsthan that of normal cells[14-16] and poor uptake due to inadequate distribution[7,14-16].

ANTIGENS

Examples are: human carcinoma associated antigens[17], p lymphoma[18], ovarian carcinoma[19], placental alkaline phosphatase, Melanoma, C-erb B-2, humanized anti-CEA antibodies.

There is no definite structure to immunoglobulin class, IgG1 and IgG2 seems to predominate as conjugate. Smaller molecules penetrate better than larger molecules in tumors due to rapid clearance[20-22].

Major problem related with mAb is that they are perceived as foreign bodies and thus limits to therapeutic efficacy. Another antibodies used for recognition processes are: single chains antibodies[23], F(ab)2 fragments[20], variable region fragments (Fv)[21]. In some cases the use of abzymes (catalytic antibodies) are designed by immunization of mice having transition state analogues but higher amounts of abzymes are needed for kinetics of the liberation[24,25]. The variation is also known as ADAPT (antibody directed abzyme pro-drug therapy)[26].

ENZYMES

There is particular characteristic for the enzymes to be used in ADEPT which includes catalyzing a cleavage reaction of the prodrug and this property must be unique from other endogenous circulating enzymes and must be stable and reactive under physiological conditions. The purpose of enzyme is to convert the inactive prodrug into active form of drug with its pH close to that of the tumor extracellular fluid. The use of enzyme with its optimum pKa outside the physiological extent provided its output is acceptable at pH 4 -7.4 is made possible by the shape of activity/pH curve.

ANTIBODY-ENZYME CONJUGATION

Linking conjugates of antibody-enzymes by chemical means uses the bifunctional reagents to link two peptides. In order to modify the side chain of protein lysine, generally one acylating group is used and further thiol group makes a link with second protein. Alternative prospective includes linkage of bispecific antibodies that recognizes both antigen and enzyme[27]. The recent advances involve recombinant fusion protein production[23, 28-30.]

By using recombinant technology[31,32] and also conventional heterobifunctional[33] reagents conjugation of antigen-enzymes have been acquired. By reacting amino acids group of antibody fragment with 5-5 acetyl thioglycolic acid N-hydroxysuccinimide ester[34] conjugates are formed and coupling with maleimide group linked to enzymes[35,33].

PRODRUGS IN ADEPT

Prodrugs are defined as a chemical entity which is inactive, but gets converted to its active form after administration due to some enzymatic action or degradation[36]. The properties to be possessed by prodrugs include, lesser toxicity than active drug, suitable substrate for enzyme under physiological conditions, should be activated only by targeted antibody-enzyme conjugate rather than host enzymes and good pharmacological and pharmacokinetic properties. The major drawback of cancer therapy is poor vascularization of tumor[15,16]. Factors which govern the uptake of drugs into the

tumor are extraction coefficient of prodrug by tumor which ultimately depends upon the chemical structure of the prodrugs, blood flow across the tumor and the probability of the drug from leaking out of tumor[18]. The consideration of time window available for therapy is the choice of prodrug-drug system[37].

Table No.1: Enzymes used in ADEPT

S.No	Enzyme system	Examples	Pro-drugs	Drugs generated	Reaction specificity
1	Enzyme with non mammalian origin with no mammalian homologues	Carboxypeptidase G2(CGP2)	Benzoic acid mustards	Mustard drugs	Cleavage of amidic, oxycarbonyl and carbamic
		ß lactamase(ß-L)	nitrogen mustardcephalosponn p-pheny!enediamine	Cephalosporin mustard (CM), 4-desacetylvinblastine-3-carboxyhydrazide, doxorubicin, taxol, mitomycin, nitrogen mustard, paclitaxel, 5-fluorouracil, Melphalan.	Cleavage of the 4-membered lactam of cephalosporin.
		Penicillin V amidase(PVA)	adriamycin-N phenoxyacetyl melphalan N-p-hydroxyphenoxy Acetamide.	Doxorubicin.	Cleavage of the phenyloxyacetamide groups linked to various substrates.
2	Enzyme non mammalian origin with mammalian homologue	ß Glucuronidase (ß-G)	p-hydroxyaniline mustard-glucuronide anthracyclineglucuronideepirubicin-glucuronide.	Camptothecin, cyclopamine, monomethylauristatin E.	Hydrolysis of b-glucose-linked residues.
		E.coliNitroreductase (NR)	5-(azaridin-1-yl-)2,4 Dinitrobenzamide.	------	Reduction of nitro groups in some aromatic systems.

Table No.2: Prodrugs used in ADEPT

Prodrugs from alkylating agents[3, 6,38-41] (enzymes activated prodrugs)[3, 6,38-41]	1.ADEPT	Assets : 1. From prodrug, per second hundreds of molecules are generated by single molecule of an enzyme. Flaws : 1. Prodrugs activation in the blood through unbound conjugates. 2. immunogenicity and conjugation heterogeneity of conjugates Assets : 1.Activation of prodrug is intracellularly 2.Preferences are given to bacterial and viral enzymes	Examples: 1. MFECP1 + ZD2767P 2. A5CP + ZD2767P 3. Vinca-cephalosporin 4. Phenylenediamine mustard-cephalosporin 5. Doxorubicin phosphate 6. Phenol mustard phosphate 7. Etoposide phosphate 8. Mitomycin C phosphate 9. Gancyclovir 5-FC
	2.GDEPT		
Prodrugs developed from antimetabolites[42-45] (Folic acid drug conjugates)	1. Prodrugs developed from Methotrexate 2. Prodrug developed from 5-Flurouracil	Advantages of using these conjugates are: 1.low immunogenicity 2.simple chemistry 5-Fluorocytosine ↓ 5-Fluorouracil (anticancer agent used in human colon cancer)	Examples: 1. TPGS-Dox-FOL (D-α-tocopheryl polyethylene glycol succinate- doxorubicin-folic acid)
Prodrugs developed from toxins[46,47] (Polymeric prodrugs)[46,47]	1.PEG- drug conjugate 2.PGA- drug conjugate 3.Polymeric drug nanoparticles	Cleavage of acetamido bond substrates Toxin ↓ acetylation Palytoxin (PTX)	Examples: 1. NHPAP (4-hydroxy phenyloxyacteamide) of PTX 2. NKTR-102 (PEGylatedirinotecan) NKTR-118 (PEG-naxol)
Prodrugs developed from antimitotic agents[48,49] (Enzymes cleavable prodrugs)	1.PSA (serin protease) 2.PSMA (prostate specific membrane antigen)	Seminal fluid PSA cleaves SeminogelinIII PSMA is a type II membrane glycoprotein	Examples: L-377202(glutaryl-Hyp-Ala-Ser-Chg-Gln-Ser-Leu-Doxorubicin)
Prodrugs developed from anthracyclins[50-53] (Peptide –drug conjugates)	Anthracyclins	Used in combination with alkaline phosphatase	Examples: 1. LHRH analog (Luteinizing Hormone Releasing Hormone) Pep42
Prodrug developed from natural anticancer products[48,54-57]	1.Mitotic poisons 2.DNA-topoisomerase inhibitors	HCN diffuses into tumor due to its lower molecular weight.	Examples: Amygdalin [(6-O-ß-D-glucopyranosyl-ß-D-glucopyranosyl) oxybenzene]-acetonitrile.

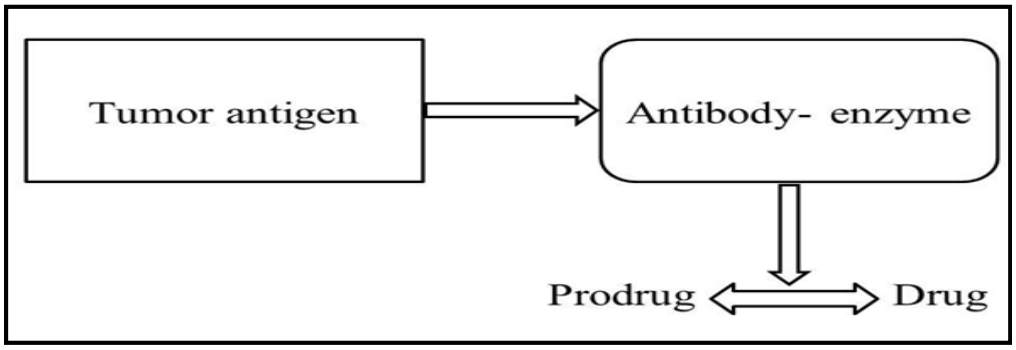

Figure No.1: Mechanism of action of antigen-enzyme conjugate

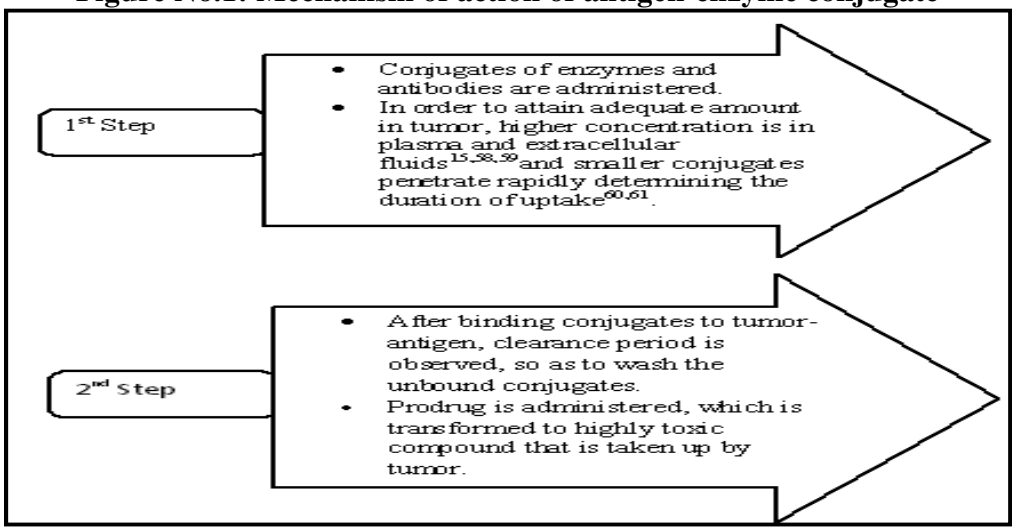

Figure No.2: Steps involved in ADEPT

CONCLUSION

ADEPT tends to be more advantageous than that of conventional cancer therapy due to following reasons: selectivity of malignant cells is increased which tends its Ab specificity; tumor cells internalizations of Ab-enzyme conjugates are not required; amplification effect is seen which leads to cleave large no. of prodrug molecule; proved to be applicable in clinic; bystander effect is seen; drugs concentration which is delivered to tumor has found to be higher than that of drug's direct injection. ADEPT has arena of research which includes: Ab-enzyme conjugates have immunogenicity and heterogeneity; use of clearance agent increases the complexity of the two step or three step system; have potential to kill normal cells due to leak back of active drug, formed at tumor.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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