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Nanocarrier mediated combination drug delivery for chemotherapy – A review

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ABSTRACT

Nanoscale delivery system has more applications in cancer treatment owing to their controlled and targeted drug release with reduced systemic cell toxicity and reduced drug adverse effects. Combination of multiple chemotherapy drugs helps to control cancer cell at different clinical stages of synergistic action, varying mechanism of action and suppressing drug resistance. Delivering drug combination chemotherapeutics in Nanocarrier base proves promising in advanced therapeutic approach on cancer cells by the enhanced pharmacokinetics of different drugs, reduced drug drug interaction and tailored drug release pattern. This article provides a brief review of various concepts behind coloading of multiple chemotherapeutic drugs in different types of nanoscale carriers and multidrug loaded nanocarriers for anticancer treatment.

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1. Introduction

Among the Common Cancer treatment like chemotherapy, radiation and surgery, Combination chemotherapy promise to show significant advantage. Combination Chemotherapy, includes co-delivery of two or more different active agents offers huge advantages for cancer treatment compared with individual agent therapy. They have different mechanism of action against cancer cells and suppress drug resistance with increased therapeutic efficacy. [1,2], Currently, many drug combinations have been approved for clinical use [3]. Combination of Daratumumab with lenalidomide and dexamethasone, or bortezomib and dexamethasone is the most recent FDA approved combination for the treatment of multiple myeloma in November 2016. Table 1 represents New drug combinations approved by FDA since 2012 [4].

Commonly known chemotherapeutic drugs are classified as alkylating agents, antimetabolites, anthracyclines, topoisomerase inhibitors, mitotic inhibitors, and corticosteroids according to their mechanism of action against cancer cells [5]. The important factors behind choosing the multiple drug combination are the stage and the type of cancer and drug-drug interaction. Variation in physicochemical property of different drug molecules may lead to complicated pharmacokinetics and pharmacodynamics in clinical trials. Many combination studies at the clinical level resulted in higher toxicity and reduced efficacy. [6] [7], This creates a major challenge for optimizing combination therapy.

Nanoscale drug delivery, commonly referred as Nanocarriers, are nanosized materials which can carry multiple drugs or imaging agents [8]. A desirable pharmacokinetic and pharmacodynamics pattern of a drug can be delivered by the nanocarrier by modifying the size and shape of the nanocarrier used. Delivering hydrophobic drug is a major advantage of nanocarriers. They enhance the dose efficacy and reduce the side effects and helps in a sustained controlled and targeted delivery of drug. These include polymer conjugates, polymeric nanoparticles, lipid-based carriers (liposomes and micelles), carbon nanotubes, and gold nanoparticles [9]. Tables 2 and 3 shown below represents Nanocarriers approved by FDA and under clinical trial for various chemotherapeutic drugs [10–12].

Research is focussed in recent years on using s nanoscale drug delivery system for multiple drug chemotherapy. Nanocarriers including Liposomes, Dentrimers, gold NPs, magnetic NPs, mesoporous silica, Polymeric nanoparticles and polymer conjugates gains much attention for combination therapy by Enhanced permeability and retention(EPR) [13] [14], They exhibit improved pharmacokinetic profiles when compared to traditional combination therapy. Proten based nanocarriers exhibit less cytotoxicity than synthetic molecules [15]. Micelles and nanotube arrays can carry hydrophilic or hydrophobic drugs depending on the orientation of the phospholipid molecules [16,17].

Although Nanocarriers are being developed to deliver multiple therapeutics with anticancer drugs, RNA, chemosensitizers, anti-angiogenic agents, this review is focused on recent research developments in delivering co-drug delivery of multiple drugs in single or multifunctional modified nanoscale platform for anticancer therapy. Fabricating nanocarrier with two or more drugs require careful selection of type of nanoscale platform and characteristics of the drug used. The ability of the nanocarrier to bind the drug(s), release the drug(s), its stability, degradation and safety are the major criteria in fabricating a nanocarrier for multidrug combination chemotherapy [11]. The resulting effect could be synergistic, additive or antagonistic.

1.1. Multi drug delivery nanoscale platforms

1.1.2. Liposomes

They are spherical in structure size ranging from 20 nm to micrometer with an aqueous core and a vesicle shell. Liposomes are

Table 1
List of FDA approved Multidrug combination for Cancer Chemotherapy.

Drug 1	Combination Drug/Drugs	Year
Daratumumab	Lenalidomide and Dexamethasone, or with Bortezomib and Dexamethasone	2016
Lenvatinib	Everolimus	2016
Obinutuzumab	Bendamustine	2016
Palbociclib	Fulvestrant	2016
Elotuzumab	Lenalidomide and Dexamethasone	2015
Necitumumab	Gemcitabine and Cisplatin	2015
Trametinib	Dabrafenib	2015
Ixazomib	Lenalidomide and Dexamethasone	2015
Irinotecan liposome[a]	Fluorouracil and Leucovorin	2015
Nivolumab	Ipilimumab	2015
Carfilzomib	Lenalidomide and Dexamethasone	2015
Ramucirumab	5-fluorouracil, leucovorin, irinotecan	2015
Panobinostat	Bortezomib and Dexamethasone	2015
Palbociclib	Letrozole	2015
Ramucirumab	Docetaxel	2014
Bevacizumab	Paclitaxel, **PEGylated liposomal doxorubicin**,[a] or topotecan	2014
Ramucirumab	Paclitaxel	2014
Idelalisib	Rituximab	2014
Ofatumumab	Chlorambucil	2014
Trametinib	Dabrafenib	2014
Obinutuzumab	Chlorambucil	2013
Pertuzumab	Trastuzumab and Docetaxel	2013
Paclitaxel (albumin-bound)[a]	Gemcitabine	2013
Bevacizumab	Fluoropyrimidine-Irinotecan or Fluoropyrimidine-Oxaliplatin	2013
Abiraterone Acetate	Prednisone	2012
Paclitaxel (albumin-bound)[a]	Carboplatin	2012
Ziv-aflibercept	5-Fluorouracil, Leucovorin, Irinotecan	2012
Cetuximab	Irinotecan, 5-Fluorouracil, Leucovorin	2012
Pertuzumab	Trastuzumab and Docetaxel	2012

[a] Nanocarrier based Drug.