Advanced Drug Delivery Reviews 115 (2017) 23–45

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Combination antitumor therapy with targeted dual-nanomedicines☆

Wenbing Dai [a], Xiaoyou Wang [a,b], Ge Song [a,b], Tongzhou Liu [a,b], Bing He [a], Hua Zhang [a], Xueqing Wang [a], Qiang Zhang [a,b,*]

[a] Beijing Key Laboratory of Molecular Pharmaceutics and New Drug Delivery Systems, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China
[b] State Key Laboratory of Natural and Biomimetic Drugs, Beijing 100191, China

ARTICLE INFO

Article history:
Received 31 December 2016
Received in revised form 24 February 2017
Accepted 3 March 2017
Available online 7 March 2017

Keywords:
Combination therapy
Dual-nanomedicines
Antitumor
Targeted nanomedicines
Cancer stem cells
Tumor microenvironment

ABSTRACT

Combination therapy is one of the important treatment strategies for cancer at present. However, the outcome of current combination therapy based on the co-administration of conventional dosage forms is suboptimal, due to the short half-lives of chemodrugs, their deficient tumor selectivity and so forth. Nanotechnology-based targeted delivery systems show great promise in addressing the associated problems and providing superior therapeutic benefits. In this review, we focus on the combination of therapeutic strategies between different nanomedicines or drug-loaded nanocarriers, rather than the co-delivery of different drugs via a single nanocarrier. We introduce the general concept of various targeting strategies of nanomedicines, present the principles of combination antitumor therapy with dual-nanomedicines, analyze their advantages and limitations compared with co-delivery strategies, and overview the recent advances of combination therapy based on targeted nanomedicines. Finally, we reviewed the challenges and future perspectives regarding the selection of therapeutic agents, targeting efficiency and the gap between the preclinical and clinical outcome.

© 2017 Elsevier B.V. All rights reserved.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Nanoformulations for combination or cascade anticancer".

* Corresponding author at: Beijing Key Laboratory of Molecular Pharmaceutics and New Drug Delivery Systems, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China.
E-mail address: zqdodo@bjmu.edu.cn (Q. Zhang).

http://dx.doi.org/10.1016/j.addr.2017.03.001
0169-409X/© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Cancer is the first leading cause of diseased-associated death in China [1] and the second leading cause of death in the United States [2] in recent years. The current treatment modalities for tumors mainly includes surgery, chemotherapy, radiotherapy, and immunotherapy, among which drug treatment is still the most widely used therapeutic mode for various types of tumors [3]. However, cancer is so complex and refractory that the efficacy of monotherapy is usually limited in clinic. Whether it is treated by conventional cytotoxic drugs or molecularly-targeted therapeutics, the drug resistance, insufficient curative effect and tumor relapse are still the huge challenges [4,5]. Take the acquired drug resistance as an example, one most common situation is that: there is good response to a therapeutic agent at the start of the treatment, but followed by a low or even no response within several cycles of treatment even with a dose escalation, leading to nearly no improvement to overall patient survival rates [6]. The resistance mechanisms include cellular factors such as over-expression of efflux transporters, defective apoptotic machineries, repair of the damaged DNA, metabolic conversion of the drug and altered molecular targets, and physiological factors such as formation of irregular tumor vasculature, higher interstitial fluid pressure (IFP) and dense extracellular matrix (ECM) [7,8].

With the increased understanding of the mechanisms underlying the compromised therapeutic efficacy of monotherapy, drug combination therapy or drug cocktail therapy is extensively exploited and increasingly becoming the standard practice to combat the cancer [9]. Combination therapy, with two or more therapeutic agents generally acting on multiple therapeutic targets, or one increasing the sensitivity of tumor cells to another one, has exhibited a promising potential in cancer therapy. In particular, with the rapid development in genomic technologies, more and more regulators of multiple signaling pathways which play key roles in oncogenic transformation and drug resistance, are identified. As a result, various kinds of inhibitors of signaling proteins or pathways are discovered and then can be used to combine with the current chemotherapeutics for cancer treatment [10].

Nevertheless, despite some foreseeable advantages compared with monotherapy, the clinical outcome of the current combination approaches based on conventional dosage forms is still unsatisfactory [11,12]. The first issue to be considered is that the possible cumulative toxicity could lead to bad patient's tolerance [13]. Besides, there are several related and perhaps interactional factors that undermine the success of current combination antitumor therapy: (a) the poor water solubility and bioavailability of active pharmaceutical ingredient (API) cause a drug level much lower than the effective therapeutic concentrations at the tumor site, (b) the short elimination half-life of API compresses the duration of efficient treatment, (c) the difference in pharmacokinetics (PK) and biodistribution of anticancer agents makes it impossible to achieve an ideal stoichiometric ratio in targeted site or exert synergistic tumor inhibition, (d) the low selectivity both in therapeutic action and spatial distribution induces inefficient therapeutic efficacy and serious toxicity, and finally, (e) the inherent biological complexity and dynamic progress of tumors often compromise the therapeutic outcome of antitumor therapy [14–16]. In fact, some advanced or refractory carcinoma does not respond to the current combinational treatments [16,17]. So, it is imperative to improve the present combinational strategies and develop new combinational options to address these pressing issues.

With the high investment and rapid development in recent years, nanotechnology has already infiltrated into all areas of biomedical science and technology [18]. Likewise, nanotechnology provides a new avenue for drug delivery, especially for tumor-targeted drug delivery. In 2004, National Cancer Institute (NCI) launched the NCI Alliance for Nanotechnology in Cancer in order to exploit the nanotechnology to combat cancer [19,20]. Targeted drug delivery system, as its name implies, is to deliver the loaded cargos to the site of interest while reducing the distribution to normal tissue or cells [21]. To date, several classes of nanocarriers have been used for anticancer drug delivery, including liposomes [22], organic, inorganic or hybrid nanoparticles [23], polymeric micelles [24], polymer-drug conjugates [25], nanogels [26], and so on (Fig. 1A). In addition to solubilizing poorly soluble drugs and protecting drug from degradation in vivo, the drug-loaded nanocarriers (recorded as nanomedicines) could prolong the circulation time of free drugs and selectively deliver them to the therapeutic target (tumor tissue, tumor cells, tumor associated stromal cells, subcellular organelle, etc.) [27]. Moreover, the release of the drugs from the nanomedicines can be controlled in a spatiotemporal manner, making the drugs exert their pharmacological activities only at the target site [28]. Some nanotechnology-based antitumor preparations, such as Doxil® (PEGylated liposomal doxorubicin (DOX)) and Abraxane® (paclitaxel (PTX) loaded albumin nanoparticles), have been approved by FDA for >10 years [29].

Based on the background and analysis above, it is rational to believe that combination therapy exploiting the nanotechnology-based targeted drug delivery is provided with great promise for cancer treatment and expected to offer superior therapeutic outcome to the current drug cocktail therapy.

There are usually three approaches for combination antitumor therapy based on nanomedicines: (1) co-administration of nanomedicine and conventional formulation, (2) co-delivery of two or more therapeutic agents (most two), in a single nanocarrier system (recorded as co-delivery), and 3) co-administration of different nanomedicines, namely the *co*-administration of different single drug-loaded nanocarriers or polymer-drug conjugates (most two, recorded as dual-nanomedicines). In view of some nanomedicines that have been approved for cancer therapy, there are already some clinical use or clinical trial using the first combinational regimen [30,31]. The nanocarrier-mediated co-delivery strategy has been widely concerned and explored since the early 21st century [32]. The loading of two or multiple drugs into a single well-designed nanocarrier might synchronize pharmacokinetics and bio-distribution of different drugs to achieve the synergistic effect [33]. This strategy has been reviewed elsewhere [11,14,34–36] recently. However, the third strategy seems to receive less attention currently. The main reason is that the studies in this regard are still in their beginning, and naturally, the comparison between co-delivery and dual-nanomedicines is rare [37]. Nevertheless, the increasing investigations showed that the strategy of dual-nanomedicines had distinct advantages for antitumor therapy, especially for targeting different cells/components in tumor microenvironment (TME) [38].

In this review, we will focus on the combination therapy strategies using separate nanomedicines, namely the dual-nanomedicines, to tackle the complexity of cancer treatment. The combination treatments with co-delivery strategy as well as those between nanomedicines and

Download English Version:

https://daneshyari.com/en/article/5519977

Download Persian Version:

https://daneshyari.com/article/5519977

Daneshyari.com