Journal of Controlled Release xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Pharmacokinetic strategies to improve drug penetration and entrapment within solid tumors

Ahmed M. Al-Abd [a,b,c], Zekra K. Aljehani [c], Rana W. Gazzaz [c], Sarah H. Fakhri [c], Aisha H. Jabbad [c], Abdulrahman M. Alahdal [c], Vladimir P. Torchilin [b,d,*]

[a] Department of Pharmacology, Medical Division, National Research Centre, Dokki, Giza, Egypt
[b] Center for Pharmaceutical Biotechnology and Nanomedicine (CPBN), Bouvé College of Health Sciences, Northeastern University, Boston, MA, USA
[c] Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia
[d] Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia

ARTICLE INFO

Article history:
Received 31 May 2015
Received in revised form 9 August 2015
Accepted 28 August 2015
Available online xxxx

Keywords:
Intratumoral pharmacokinetics
Angiogenesis inhibitors
Vascular disrupting agent
Tumor priming
Metronomic therapy
Chemoembolization
P-glycoprotein inhibitors
Extracellular matrix dissolving agents

ABSTRACT

Despite the discovery of a large number of anticancer agents, cancer still remains among the leading causes of death since the middle of the twentieth century. Solid tumors possess a high degree of genetic instability and emergence of treatment resistance. Tumor resistance has emerged for almost all approved anticancer drugs and will most probably emerge for newly discovered anticancer agents as well. The use of pharmacokinetic approaches to increase anticancer drug concentrations within the solid tumor compartment and prolong its entrapment might diminish the possibility of resistance emergence at the molecular pharmacodynamic level and might even reverse tumor resistance. Several novel treatment modalities such as metronomic therapy, angiogenesis inhibitors, vascular disrupting agents and tumor priming have been introduced to improve solid tumor treatment outcomes. In the current review we will discuss the pharmacokinetic aspect of these treatment modalities in addition to other older treatment modalities, such as extracellular matrix dissolving agents, extracellular matrix synthesis inhibitors, chemoembolization and cellular efflux pump inhibition. Many of these strategies showed variable degrees of success/failure; however, reallocating these modalities based on their influence on the intratumoral pharmacokinetics might improve their understanding and treatment outcomes.

1. Failure of solid tumor treatment: influence of poor intratumoral pharmacokinetics

Despite the discovery of several agents with potential anti-solid tumor activity at both pre-clinical and clinical levels, no significant change in the global statistics of cancer-related mortality was noticed since the 1950s [1–6]. Yet, great concern was directed to pharmacokinetic approaches (drug delivery) beside pharmacodynamic discoveries (new drug molecules or novel targets). Any anticancer drug must be available at the site of action in suitable concentration to exert its designated effect. This basic pharmacokinetic principle is considered as an essential barrier for solid tumor treatment [7,8]. In contrast to all normal body tissues, the solid tumor microenvironment is poorly perfused with blood due to crowded tumor parenchyma, collapsed intratumoral blood vessels, extensive extracellular matrix (ECM) components and elevated interstitial fluid pressure (IFP) [9–11]. Regardless of the preferential accumulation of drugs and macromolecules in the tumoral blood vessels due to enhanced permeation and retention (EPR) effect, homogenous intratumoral distribution is not guaranteed [9,12,13]. In other words, EPR is not the end of the story; it is the start of another challenge [14]. Packing density of solid tumor cells has been shown to significantly influence the intratumoral drug distribution [15–17]. In addition to the cellular component of the solid tumor microenvironment, non-cellular components such as ECM significantly influence intratumoral drug distribution [9,18]. It looks like solid tumor treatment resistance might be to a great extent attributed to pharmacokinetic reasons at both localized (intratumoral pharmacokinetics) and systemic levels (whole body pharmacokinetics) in addition to the classic molecular events [19–22]. Herein, we are presenting different pharmacokinetic approaches/strategies to improve intratumoral penetration, delivery, distribution and retention within solid tumor micro-regions.

2. The influence of angiogenesis inhibition on the intratumoral pharmacokinetics

Intratumoral angiogenesis is the process of developing a new vascular network from a pre-existing vascular bed within the growing tumor

Abbreviations: ECM, extracellular matrix; IFP, interstitial fluid pressure; EPR, enhanced permeation and retention; AI, angiogenesis inhibitors; VEGF, vascular endothelial growth factor; VDA, vascular disrupting agent; CEP, circulating endothelial progenitor; TACE, transarterial chemoembolization; P-gp, permeability glycoprotein; MDR, multidrug resistance protein.

* Corresponding author at: Center for Pharmaceutical Biotechnology and Nanomedicine (CPBN), Bouvé College of Health Sciences, Northeastern University, Boston, MA, USA.
E-mail address: v.torchilin@neu.edu (V.P. Torchilin).

http://dx.doi.org/10.1016/j.jconrel.2015.08.055
0168-3659/

tissue [23]. This process involves the recruitment of the host vasculature and vascular progenitor cells to generate new blood vessels. These newly formed blood vessels are originally made to meet the excessive nutritional and oxygen demand for tumor growth [24,25]. Blocking this process with angiogenesis inhibitors (AI) appeared as a brilliant idea to prohibit the delivery of nutrient and oxygen supplies to tumor parenchyma leading to their death on their own; a process could be named as "tumor under siege" [26]. The blockade of tumoral angiogenesis is primarily achieved via inhibiting the release of pro-angiogenic factors, such as the vascular endothelium growth factor (VEGF), from the avascular tumor microenvironment [25,27]. However and due to the excessive tumor cell proliferation, the intratumoral vasculature is known to be compressed, non-functioning, abnormal, and immature with a chaotic structure (Fig. 1-A). These unique intratumoral vascular peculiarities result in unique intratumoral microenvironment conditions in terms of acidosis, hypoxia, and elevated interstitial fluid pressure (IFP) [28,29]. Therefore, proper delivery of chemotherapeutic agents into solid tumor tissues is dramatically hindered [30]. Putting in consideration the influence of the intratumoral blood vessel structure and functionality in intratumoral delivery, AI might significantly affect its own intratumoral pharmacokinetics as well as any simultaneously administered anticancer drug [31,32]. In the current section, we will discuss the local pharmacokinetic influence of AI and related treatment modalities within solid tumors (Fig. 1).

In contrary to what might come to mind, multiple evidences showed that angiogenesis inhibition enhanced the intratumoral distribution and delivery of drugs. This was associated with reducing the intratumoral vascular density accompanied by morphological and functional maturity collectively named as "intratumoral vascular normalization". This vascular normalization results in better perfusion and improved drug delivery and efficacy [33,34]. Excessive exposure to AI results in complete vascular shut down and ablated intratumoral delivery (Fig. 1-C). Accordingly, intratumoral vascular normalization takes place within a certain exposure window of time and concentration. The vascular normalization window refers to the specific time period after exposure to AI during which intratumoral vasculature demonstrates features of the normalization [35,36]. Studies of murine and human tumors suggested the avascular normalization window to take place within 1–2 days after angiogenesis inhibition [37]. This was shown in the vascular normalizing effect of DC-101, an angiogenesis inhibitor, which improved the pressure gradient across the intratumoral blood vessels and enhanced intratumoral drug penetration resulting ultimately into superior efficacy against colorectal carcinoma [38–40]. Determining the normalization window for each agent in terms of dose and time lap is critical for optimum clinical outcomes [41]. Besides, normalization is not guaranteed as a delivery enhancer for all drugs with different molecular sizes (especially macromolecules) [42].

In addition, the response to radiotherapy during the normalization window induced by DC-101 was significantly higher [43]. This might be attributed to better oxygenation of the intratumoral microenvironment due to improved vascularization and blood perfusion. The antiangiogenic agent, bevacizumab (anti-VEGF monoclonal antibody),

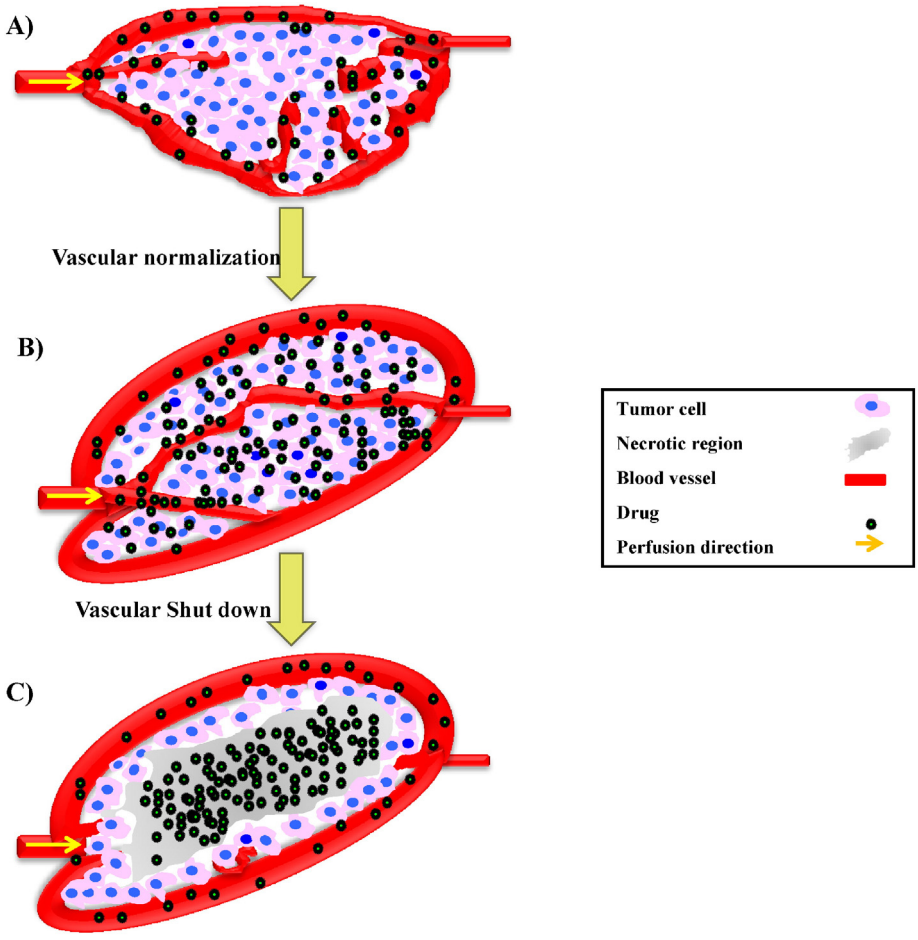

Fig. 1. Diagrammatic illustration for the influence of interfering with the intratumoral blood vessels on the local pharmacokinetics. The primary response of the interrupted poorly perfused intratumoral blood vessels (A) to treatment with AI or after metronomic therapy appears in the form of vascular normalization (B). Further doses of AI or VDAs result in complete shut down for the intratumoral vascular bed (C).

Please cite this article as: A.M. Al-Abd, et al., Pharmacokinetic strategies to improve drug penetration and entrapment within solid tumors, J. Control. Release (2015), http://dx.doi.org/10.1016/j.jconrel.2015.08.055