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Nanocarriers in cancer clinical practice: a pharmacokinetic issue

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Abstract

The advent of nanocarriers for drug delivery has given rise to new intriguing scenarios in the cancer field. Nanocarriers indeed partly overcome the limits of traditional cytotoxic drugs principally changing the pharmacokinetic behavior of the parental drug. The peculiar characteristics of these systems strongly minimize the adverse reactions and ensure a more precise release of the compound to the tumor site. Several nanocarriers have been developed for the delivery of cytotoxic drugs such as paclitaxel and doxorubicin in order to improve both the outcome and the patients' quality of life. The aims of this review are to describe in detail the pharmacokinetics of nanocarriers, already marketed or in advanced clinical phases, for paclitaxel and doxorubicin, to highlight the main differences with the parental drugs, and to underline, in a critical manner, benefits and disadvantages related to the use of these new drug delivery systems.

Keywords: Nanocarrier; pharmacokinetics; cancer; paclitaxel; doxorubicin

Pharmacokinetics (PK) is a branch of pharmacology that describes the fate of administered drugs through the study of their absorption, distribution, metabolism, and excretion (ADME). A precise determination of the PK is fundamental to provide the rational basis for the drug formulation, the definition of an appropriate use of the drug and for the clinical trial design.

PK plays an important role in the cancer field, in which the frail equilibrium between ADME processes and drug efficacy/toxicity could be a hurdle for the finalization of the treatment.

The main pharmacokinetic parameters that describe the ADME processes are reported in Table 1. They include the maximum plasma concentration and the time at which this concentration is reached (C_{max} and T_{max}, respectively), the area under the concentration-time curve (AUC), the volume of distribution (V_d), the half-life ($t_{1/2}$), and the clearance (Cl) of the drug.[1]

A plethora of factors such as genetic differences in genes involved in drug metabolism, body size, ratio of fat to total mass, abnormalities in liver or kidneys functions, and co-morbidity can influence these parameters and give rise to an important inter- and intra-patient variability in the response to treatments.[2]

Moreover, traditional anticancer drugs are characterized by a narrow therapeutic window meaning that relatively small changes in drug disposition may lead to a lower drug activity or extreme toxicities, seriously affecting both the outcome and patient's quality of life.

In order to overcome these problems and to improve the PK of the traditional antineoplastic drugs, new technologies have been investigated. In particular, nanocarrier systems for the delivery of cytotoxic agents have strongly changed the pharmacokinetic behavior of the parental drugs due to their peculiar chemical and physical characteristics. Therefore, due to the crucial role of the physicochemistry of nanocarriers, we dedicate a specific section to briefly describe the main characteristics that modify their kinetics.

Main aspects that influence the nanocarrier kinetics

The main aspects influencing the nanocarrier kinetics are the particle size, the shape, the surface charge, and the surface modifications.[3]

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Table 1
Description of the main pharmacokinetic parameters that characterize the ADME processes.

Parameter	Definition
C_{max} (maximum plasma concentration)	The highest concentration observed in plasma
T_{max} (time until $C_{max}$is reached)	The time at which the C_{max} is reached
AUC (area under the concentration-time curve)	The actual body exposure to treatment after administration of a dose of the drug
AUC_{0-t}	AUC from time 0 to time t after the start of the administration
AUC_{inf}	AUC from time 0 to infinity
V_d (volume of distribution)	The hypothetical volume of body fluid that would be required to dissolve the total amount of drug needed to achieve the same concentration as that found in the blood
$t_{1/2}$ (half-life in the terminal phase)	The time required to reduce the plasma concentration to one half
Cl (clearance)	The rate of drug elimination by all routes (especially hepatic and renal) normalized to the concentration of the drug

Size

The size strongly influences the kinetics and the tumor accumulation of nanocarriers. In fact, they need to be smaller than the cut-off of the fenestration in the neovasculature (250-500 nm) in order to pass through tumor vessels and concentrate in the target site.[4] On the one hand, the lower size limit should prevent the random penetration of the nanocarriers in the normal vessels and evade their capture by the reticuloendothelial system (RES). On the other hand, when size is increased, a high drug-storage capacity is guaranteed but, at the same time, the risk of being recognized by the RES increases, too.[5]

Shape

The shape has been shown to influence the blood exposure of nanocarriers by modulating their interaction with the mononuclear phagocyte system (MPS) and their body distribution. Findings in the literature suggest, for example, that elongated shapes (e.g. nanotubes or nanorods) might present beneficial enhanced permeability and retention (EPR) properties and seem to remain in the blood longer than their spherical counterparts.[6] Moreover, changing the nanocarrier shape can modulate the distribution of particles throughout the circulatory system. For example, intravenous injection of particles will result in varying distribution and circulation when comparing different shapes.[7] For instance, rod shaped particles appear to have high adhesion properties and could be used to target particles to the endothelium junctions while discoidal particles seem to accumulate less in the liver but can reach the lungs and other organs.[8]

Surface charge and modification

The charge of nanocarriers could alter both the systemic circulation time and intratumoral processes. In particular, the surface charge can alter the opsonization profile, the mononuclear phagocyte system recognition and the overall plasma circulation. The neutral formulations are typically characterized by an increased aggregation and a reduced physical stability and, due to their weak interaction with cells, they tend to release the drug in the extracellular space.[9] On the other hand, charged nanocarriers lead to an electrostatic repulsion among them and prevent their aggregation. However, negatively charged formulations seem to be less stable than neutral or positively charged formulations when injected in blood circulation because of a rapid uptake by the RES and toxic effects such as pseudo allergy.[10]

Regarding the surface modification, the conjugation on the nanocarrier surface of a polyethylene glycol chain (PEGylation) represents one of the principle strategies to improve their stability. These chains indeed can be used to cover any undesired charge or surface properties in order to prolong the circulation time and avoid the recognition of the peculiar nanocarrier charge by opsonin proteins.[11]

In Figure 1 the major benefits derived from the modulations of the characteristics described above are schematized: 1) extended blood circulation time (longer $t_{1/2}$), 2) enhanced immune system escape, 3) decreased RES Cl, 4) reduction of the V_d, 5) increased biocompatibility and consequent decreased of the drug-related toxicity,[12] and 6) accumulation *in loco* via EPR effect. This latter phenomenon improves the passive delivery by allowing nanocarriers to accumulate into solid tumors: in pathological conditions like cancer, local vessels are more permeable due to the increased size of endothelium fenestration. Through these leaky vessels, nanocarriers can extravasate and reach the tumor site, where they tend to reside due to the scarce lymphatic drainage.[3]

The EPR effect underlies the development of several nanocarriers already marketed. The first generation of these systems is indeed based on the passive targeting strategy that depends on the longevity of the pharmaceutical carrier in the blood and its accumulation in pathological sites with compromised vasculature.[3]

On the contrary, latest generations of nanocarriers are mainly based on the active targeting strategy. In this case, high affinity ligands are linked to the surface of nanocarriers to improve the selective targeting of the drug. This approach aims to increase the interactions between nanocarriers and cells, thus enhancing the internalization of the drug in the tumor cell.[3] Finally, in the last years, innovative strategies called stimuli-responsive systems