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Review article

Mathematical models of the steps involved in the systemic delivery of a chemotherapeutic to a solid tumor: From circulation to survival

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ABSTRACT

The efficacy of an intravenously administered chemotherapeutic for treatment of a solid tumor is dependent on a sequence of steps, including circulation, extravasation by the enhanced permeability and retention effect, transport in the tumor microenvironment, the mechanism of cellular uptake and trafficking, and the mechanism of drug action. These steps are coupled since the time dependent concentration in circulation determines the concentration and distribution in the tumor microenvironment, and hence the amount taken up by individual cells within the tumor. Models have been developed for each of the steps in the delivery process although their predictive power remains limited. Advances in our understanding of the steps in the delivery process will result in refined models with improvements in predictive power and ultimately allow the development of integrated models that link systemic administration of a drug to the probability of survival. Integrated models that predict outcomes based on patient specific data could be used to select the optimum therapeutic regimens. Here we present an overview of current models for the steps in the delivery process and highlight knowledge gaps that are key to developing integrated models.

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Fig. 1. The systemic delivery and action of a drug or drug delivery vehicle to treat a solid tumor involves several steps. Following injection, the time dependent distribution of the drug in circulation is described by the pharmacokinetics. The extravasation of the drug from circulation at the tumor site is usually governed by the enhanced permeation and retention effect. On exiting circulation at the tumor site, transport in the extracellular matrix is followed by uptake in the target cells. The delivery of the drug to the target compartment in a cancer cell depends on the state of the drug (e.g. pro-drug, conjugated to an antibody or delivery vehicle by a linker, or contained in a liposome or other nanoparticle), the mechanism of uptake by the target cell, and the mechanism of action of the drug. Arresting or reversing tumor growth is dependent on the preceding steps. Survival is dependent primarily on the efficiency of the preceding steps, and may be coupled with other interventions such as radiation therapy or resection. Survival may be negatively impacted by unwanted side effects associated with uptake in normal tissue.

1. Introduction

The systemic delivery of a drug to a solid tumor involves several steps which occur in series and ultimately determine drug efficacy (Fig. 1). On administration, the time dependent drug concentration in blood is described by the pharmacokinetics. In many cases simple one-compartment or two-compartment models can be used to describe the blood concentration of the drug or delivery system. The extravasation of a drug from circulation at a tumor site is usually determined by the enhanced permeability and retention (EPR) effect. Following extravasation, a drug can undergo passive transport in the extracellular matrix before uptake by cells in the tumor microenvironment. Convection may also contribute to transport in the extracellular matrix if there is interstitial flow. After internalization the drug is delivered to the appropriate compartment by intracellular trafficking. For pro-drugs or nanomedicines, drug release represents an additional step in the drug delivery process. Drug delivery to a tumor cell may induce apoptosis or inhibit proliferation, thereby modulating tumor growth rate and hence tumor size. Modulating tumor growth impacts the ultimate probability of survival.

While this summary is simplistic and neglects a number of important factors, it represents the important steps that link the systemic administration of a drug to the probability of survival. Each step in the process is the subject of intense research including both experiment and modeling. Models include pharmacokinetic, physiological, numerical and analytical models, and span length scales from nanometers to meters (Table 1). Models for individual steps are frequently empirical but have been refined with input from pre-clinical or clinical trials to provide predictive power.

Integration of physiologically-based pharmacokinetic models, with models of extravasation from the tumor vasculature, and models that describe transport, uptake, and trafficking in the tumor microenvironment, have the potential to model changes in tumor growth rate and ultimately, survivability. Here we assess the feasibility of integrating models for the individual steps in the drug delivery process (Fig. 1) into models that can predict patient outcomes. We summarize the current models and highlight the knowledge gaps that are key to developing integrated models that can link administration to survival. In the future, with advances in our understanding of the steps in the delivery process and the development of more predictive models, it will be possible to use patient specific data to select drug and dosing regimens to optimize tumor growth trajectories and outcomes.

2. Pharmacokinetics

2.1. Pharmacokinetic models

The uptake, distribution, and elimination of a drug are dependent on a wide range of physiological factors. To overcome the complexities in modeling these physiological interactions, the pharmacokinetics of a drug or drug delivery system are usually described by empirical models [1]. In many cases, the pharmacokinetics of a systemically administered drug can be analyzed using a one- or two-compartment model assuming first order rate constants (Fig. 2A) [1]. Analysis of the drug concentration in blood or plasma with time can be used to extract parameters such as area under the curve (AUC), clearance rate, distribution volume, and elimination half-time. These models are relatively easy to use and an invaluable tool in providing global insight into the distribution and elimination of a drug.

2.2. Physiologically-based pharmacokinetics

While these empirical models are useful in developing therapeutic strategies and in comparing drugs, they have limited predictive power. The recent emergence of physiologically-based pharmacokinetic (PBPK) models holds promise for the prediction of pharmacokinetic parameters, and is an important step in the development of integrated cancer therapy models [2]. The classical two-compartment PK models divide the body into the vascular system and highly perfused tissues (the central compartment) and normal tissue (peripheral compartment). PBPK models consider blood perfusion throughout all organs and tissues of the body. The complexity of each organ compartment may vary from a simple perfusion rate limited model to more detailed models that take into account cellular and molecular level processes involved in drug binding and transport, such as plasma-protein binding affinities, membrane permeability, enzymatic stability, and

Table 1
Models for steps in the systemic delivery of a drug to a solid tumor.

Step	Models	Features	Length scale
Circulation	• Pharmacokinetic • Physiologically-based pharmacokinetics (PBPK)	Vasculature/organs	Total length: 10^5 km diameter: 5 μm–1 cm
Extravasation (EPR effect)	• Kinetic	Typical vessel spacing (tumor) Typical vessel diameter (tumor) Paracellular defect (tumor) Total vessel length in tumor (150 mm mm^{-3})	100–200 μm 20–30 μm ≤1 μm 100 m
Transport	• Numerical	Maximum diffusion length (half average distance between vessels)	50 μm–100 μm
Uptake, trafficking		Sub-cellular (endocytosis, phagocytosis, etc.)	1 nm–10 μm (cell)
Tumor growth	• Empirical • Metabolic	Cellular	10 μm–1 cm (tumor)