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Perspective review

Mind the gap: A survey of how cancer drug carriers are susceptible to the gap between research and practice

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ABSTRACT

With countless research papers using preclinical models and showing the superiority of nanoparticle design over current drug therapies used to treat cancers, it is surprising how deficient the translation of these nano-sized drug carriers into the clinical setting is. This review article seeks to compare the preclinical and clinical results for Doxil®, PK1, Abraxane®, Genexol-PM®, Xyotax™, NC-6004, Mylotarg®, PK2, and CALAA-01. While not comprehensive, it covers nano-sized drug carriers designed to improve the efficacy of common drugs used in chemotherapy. While not always available or comparable, effort was made to compare the pharmacokinetics, toxicity, and efficacy between the animal and human studies. Discussion is provided to suggest what might be causing the gap. Finally, suggestions and encouragement are dispensed for the potential that nano-sized drug carriers hold.

Contents

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1. Introduction

Nanotechnology is a remarkable example of human achievement. In only a few decades of concerted effort, our knowledge of the laws of physics and chemistry has expanded to the point that we are able to manipulate matter at nearly the atomic scale to create complex structures with unique and potentially revolutionary functions. Nanotechnology describes the ability to manipulate matter at the scale of 1–100 nm in order to create and use structures with new, unique and useful properties [1]. This technology has far-reaching implications for improving the human condition, including more compact and powerful microchips and processors, more robust agriculture, cleaner, more efficient fuels, and better health. With this promise in mind, billions of dollars have been invested in nanotechnology research, and in some fields the return of that investment is starting to be realized [2]. However, as with most new technologies, progress has been uneven and the nature of future advancements uncertain.

Nanomedicine is the application of nanotechnology to improve the health of individuals through better diagnoses and treatments. However, nanomedicine is a very broad term, including applications in sensors, tissue engineering, imaging agents and other diagnostics, lab-on-a-chip devices, therapeutic agents, and drug carriers. Its usefulness has been diluted by a degree of irrational exuberance that has permeated the discussion of nanotechnology over the last few decades [2–12]. Furthermore, certain technologies such as liposomes, polymer therapeutics, and protein therapeutics have existed long before "nanotechnology" was introduced. Thus, when considering drug delivery technology, particularly for anti-cancer therapeutics, it may be useful to abandon the term nanomedicine and instead adopt less loaded descriptors. This review will refer to these technologies as nano-sized drug carriers or simply drug carriers which are injectable into the blood stream, and focus on those drug carriers which were designed to provide better efficacy and lower toxicity for cancer therapeutics. The impact of drug carriers has in some ways been difficult to judge; they can be quite versatile, allowing researchers the flexibility to design delivery strategies specific to environmental challenges posed by the body. On the other hand, the more complex designs have thus far had little impact on clinical therapies beyond merely adding the rhetoric of targeted drug delivery to somewhat conventional therapies.

Cancer has been an area of particular interest for nano-sized drug carriers due to the enhanced permeability and retention (EPR) effect which is thought to provide them with significant therapeutic advantages over small molecule chemotherapy drugs [13,14]. EPR refers to the tendency for nanoparticles and macromolecules to accumulate in tumors more, in comparison with the control solution formulations, due to the disorganized and ill-formed blood vessels that contain large fenestrae through which these large molecules can pass. Retention is increased by the dysfunctional lymph vessels which significantly hinder drainage from the tumor interstitial space. EPR was first discovered in the 1980s by Dr. Hiroshi Maeda and has subsequently become a key concept in the field of cancer drug delivery [15,16]. According to the EPR hypothesis, nano-sized drug carriers should enjoy a natural advantage over traditional therapies as the increased drug concentration within a tumor should provide improved efficacy, and reduced toxicity due to the shielding of the drug from the rest of the body. This has generally been the case in the animal models used for preclinical studies [17–20], but the improved efficacy promised by the EPR effect has often failed to materialize in clinical settings [21,22].

The apparent gap between preclinical animal models and the clinical tumors encountered by clinicians is of great interest if drug carriers are to make a significant impact at the core of cancer therapy rather than just at the margins. Oncology drugs (including drug carrier technologies) suffer a 95% failure rate after entering human trials. Most of these failures occur in the efficacy phases and can cost hundreds of millions of dollars. A better understanding of the shortcomings of commonly used models could thus potentially save billions of dollars in wasted effort.

This review presents a cross section of some of the most important formulation strategies being pursued by researchers including liposomal formulations, micelles, linear polymers and protein carriers. Each of these formulations is unique in the way it changes the interactions between the drug and body. Some are designed with a half-life of several days, leaving a portion to circulate for weeks in the blood, with the intent to slowly accumulate in the tumor *via* EPR. Others simply attempt to improve the solubility of the drug cargo without harmful effects. Still others seek to actively target tumors by attaching groups that participate in ligand binding events with either cancer cell surface proteins or other targets of interest. Most of these formulations drastically impact how the drug and body interact, including starkly different pharmacokinetic parameters such as half-life, area under the curve, distribution, and clearance. Curiously, however, the impact of these formulations on efficacy is rarely significant outside the laboratory (Fig. 1).

Comparing human tumors to animal models can be a difficult game. In addition to the obvious differences in size, lifespan, physiology and

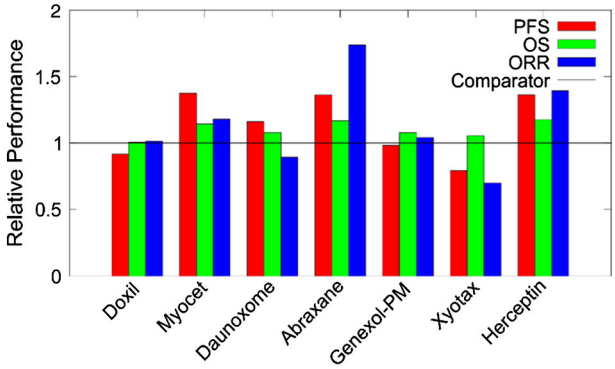

Fig. 1. Summary of phase III performance of selected drug carrier therapies compared to standard treatment. PFS: progression free survival; OS: overall survival; ORR: overall response rate. Data gathered from phase III trials [21,22,69,106,119,122,183–185].

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