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Review of the Clinical Trial Failures of Nanomedicines Targeting Cancer

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ABSTRACT

Nanomedicine offers the potential to increase drug delivery to therapeutic targets while simultaneously reducing the instances of detrimental side effects. However, nanoparticles undergoing clinical trials are plagued with failures. One potential reason for such a high attrition rate is that proposed nanoparticle designs are based on models in preclinical trials which do not translate well to human clinical trials. Additionally, many cancer drugs suffer from a high excretion rate or, their dose-limiting toxicity prevents them from delivering an effective amount of therapeutic agent. Such failures are exemplified by BIND Therapeutics and Cerulean Pharma. This review article will attempt to detail the issues with model organisms encountered in translational research, as well as give a potential reason by comparing the failures of CRLX101, CRLX301, and BIND-014 with the success of Abraxane using the maximum tolerated dose (MTD) as a differentiating parameter.

Introduction

Nanomedicine is defined as the application of principles of nanotechnology to the diagnosis and treatment of diseases in a living organism (Soares, 2018). Nanomedicine is used in a variety of applications, yet one of its main promises is its ability to treat cancer. These treatments function via the enhanced permeability and retention effect (EPR). The EPR occurs due to a unique feature of tumors in that they are hypervascularized and these blood vessels leading to the tumor are hyperpermeable. Additionally, poor lymphatic drainage allows for the consistent accumulation of fluids and macromolecules near the sites of tumors and within tumors themselves (Prabhakar et al., 2014, Matsumura & Maeda, 1986). There are size restrictions, as the pores in tumor vasculature are only able to accommodate nanoparticles below 600 nm in diameter (Yuan et al., 1995). Nanomedicine aims to take advantage of the EPR to simultaneously increase the delivery of a therapeutic agent to tumors and reduce collateral damage in the form of the loss of normal cells.

There are various types of nanoparticles, each with unique characteristics. One common formulation is the liposome. A liposome consists of at least one phospholipid layer, making different liposome formulations able to encapsulate either hydrophobic or hydrophilic cancer formulations. Liposomes can have antigens attached to their surface for active targeting of a disease, are biocompatible, and generally reduce the side effects of chemotherapy agents(Akbarzadeh et al., 2013), (Rafiyath, 2012). An alternative strategy to the liposome is to use albumin-bound drugs. Human serum albumin is a protein that binds to hydrophobic molecules and allows them to be transported inside the blood (Pappa & Refetoff, 2017). Using this property of albumin, researchers were able to attach paclitaxel (a hydrophobic drug) to albumin to increase efficacy and reduce toxicity (Desai et al., 2006). In addition to this, cancer cells preferentially uptake albumin due to the EPR effect, furthering its potency as a drug delivery mechanism (Hoogenboezem & Duvall, 2019). It also circulates in the bloodstream longer than liposomes due to active reuptake in nephrons (Hoogenboezem & Duvall, 2019). Additional formulations of nanoparticles include attaching polyethylene glycol (PEG) to another nanoparticle formulation (for example, a liposome coated in PEG). PEG is a non-immunogenic, non-toxic polymer that reduces immunogenicity, renal excretion, proteolysis, and improves drug solubility as well as retention time (Veronese & Mero, 2018). Additionally, it is possible to formulate nanoparticles using cyclodextrins, which are glucopyranosides bound together in a ring configuration (Young et al., 2011). This arrangement forms

a truncated cone, in which hydrophobic molecules can be attached to form a drug delivery mechanism (Cyclodextrins, 2015). Other formulations include iron oxide nanoparticles and gold nanoparticles (Magforce: Our Therapy, 2022), (Sztandera et al., 2018).

Despite its promising hypothesis, nanoparticles approved for treating cancer have very low success rates from preclinical trials to clinical trials. In 2019, there were 190 ongoing and completed clinical trials involving nanomedicine. The success rate of phase I clinical trials was high, at approximately 94%. These numbers drop significantly, with the success rate of phase II clinical trials being approximately 48%, and that of phase III trials being 14% (Hongliang et al., 2019). Thus, despite the enthusiasm surrounding the future developments of nanoparticle formulations for treating cancer, there is a definite point of failure between preclinical and clinical trials. This literature review attempts to identify potential reasons for the discrepancy in success rates.

Methods

This paper consists of a literature review based on papers that are relevant to the topic. While searching, keywords and key terms were used to help narrow down the list of relevant references. The most common of these were 'nanoparticle' and 'cancer'. Additionally, the articles considered were usually published within the last 7 to 8 years. Many of these articles were in peer-reviewed journals, such as Nature Publishing Group, Elsevier, SAGE Publications, ACS Publications, and NCBI. To determine if an article was relevant, the title and abstract were read with care, and only then was it decided to read further. If the abstract was deemed irrelevant, the search would be repeated, moving to another article. If the article passed the test for relevance, then it was read carefully, while noting what each of the author's key points was. Since many clinical trials were encountered during the search, technical terms were encountered with frequency, the majority of which had to be looked up.

Results

Several of the clinical trials, as aforementioned, are failures due to a lack of efficacy (Hongliang et al., 2019). While there could be many possible explanations why each clinical trial did not succeed according to the original goals, this review article will focus on only a few.

BIND Therapeutics

The stated reason for the failure of BIND-014 is that its drug delivery platform (ACCURINS) did not meet or exceed the overall response rate (ORR) required to continue enrolling patients in its clinical trial (FORM 8-K, 2015). The phase I study suggested an MTD of 60 mg/m^2 tri-weekly or 40 mg/m^2 per week (Hoff et al., 2016).

Cerulean Pharma

The stated reason for the failure of CRLX 101 was that it failed to improve the life expectancy of patients compared to best supportive care. Cerulean did not disclose other relevant measurements, such as safety, objective tumor response, and progression-free survival of patients (UPDATED: Cerulean Pharma's Lead Nanodrug Crashes in Lung Cancer Study, 2013).

These two failures are publicized examples of the overall failures of cancer nanomedicine clinical trials. Since Doxil ® was approved by the FDA in 1995 (Barenholz, 2012), there have been another 19 approved nanomedicines over the last years, yet that does not accurately reflect the time and money invested in such undertaking (Barenholz, 2021), (Bhardwaj, 2019).

Recommendations

One possible reason for such a disconnect between the preclinical trial results and the clinical trials of nanoparticles is simply the difference between mice and humans. Animals have been used as test subjects since 1937, when the Elixir Sulfanilamide tragedy gave rise to the 1938 Food, Drug, and Cosmetic Act, which necessitates animal testing on cosmetics and drugs as well as having labels on them for safe use (Ballentine, 1981).

However, animal testing is somewhat flawed, simply because animals are not fully representative of humans. For example, Hodge et al. used snRNA sequencing to determine expression levels of certain genes in the mouse and human brain (Hodge, 2019) and found that many genes are differentially expressed, thus leading to treatments that function in mice yet are unable to function similarly in humans. As one example of this difference, the trials of TGN1412 failed to accurately predict the effects TGN1412 had on the human body. The drug is a superagonist monoclonal antibody, able to directly stimulate T cells in vivo, as a treatment for arthritis and chronic lymphocytic leukemia (Nemenov, 2017), (Horvath & Milton, 2009). The monoclonal antibody binds to the CD28 receptor on T cells (Lühder et al., 2003) and stimulates their immune system. The preclinical trials of the drug in cynomolgus macaques showed no signs of toxicity or system-wide T-cell activation (Eastwood et al., 2010), thus lending credence to the idea that this drug could safely be administered to humans. In the clinical trial, six men (median age 29.5 years) received 0.1 mg TGN1412 per kg body weight. There were severe side effects, such as headaches, hypotension, tachycardia, and multiorgan failure (Suntharalingam et al., 2006). The severe side effects observed in humans can be explained because cynomolgus macaques do not express CD28 on T-cells (Eastwood et al., 2010).

A few key methods of improving preclinical studies are decreasing variability as well as reducing bias. For example, variability might be decreased if all animals are relatively similar, and exposed to the same environments and procedures. Reducing bias could be done by refocusing on investigator blinding. Small, preclinical studies also suffer from sensitivity to missing data, and as such, there should be a method to handle such an occurrence.

Methods to reduce clinical trial failures due to inaccurate modeling do exist. Organ-on-chip technologies use human cells and microfluidics to mimic organ systems to determine the toxicity of drugs (Ingber, 2022). This averts many pitfalls of animal testing as human cells are being used, with the surrounding environment mimicking the extracellular space of an organ. In silico testing is another viable option of reducing animal testing, by using computer models of drugs to effectively screen a large sample of molecules without having to resort to expensive high-throughput screening (Raunio, 2011). Additionally, as our knowledge of biological systems improves, and as computers increase in power, the predictive power of in silico models will improve.

Another possibility for the failures in clinical trials could be that the amount of therapeutic agent reaching the tumor is insufficient. A recent study has shown that on average, approximately 0.7% of the injected chemotherapy manages to reach a cancerous tumor (Wilhelm, 2016). As such, if a medication has a low MTD, then there will probably not be enough therapeutic agents to elicit a clinically significant response. The below examples with calculations illustrate why.

BIND-014:

BIND-014 was a nanoparticle formulation that promised to be effective in treating prostate cancer using docetaxel, a well-used drug in treating solid tumors. The phase 1 study showed that the MTD of BIND-014 was 60 mg/m^2 (Hoff et al., 2016). The molecular weight of docetaxel is 807.9 grams/mol (*Compound Summary - Docetaxel*, n.d.), which results in the MTD of docetaxel encapsulated in BIND-014 equal to 0.00007427mol/m^2 as shown below.

Equation 1: Calculations of MTD in moles of docetaxel in BIND-014

$$\frac{60\ mg}{m^2}(MTD\ of\ BIND-014)*\frac{1\ mol}{807.879\ g}(molar\ mass\ of\ docetaxel)*\frac{g}{1000\ mg}$$
$$=0.00007427\ \frac{mol\ docetaxel}{m^2}$$

CRLX-101 and CRLX-301:

Cerulean Pharma (now defunct) had quite a few drugs in clinical trials using a cyclodextrin-PEG formulation to deliver drugs, such as camptothecin and docetaxel (Young et al., 2011)(Lazarus et al., 2012). The phase 1 study for CRLX-101 and CRLX-301 showed that both drugs had a MTD of 15 mg/m^2 (Weiss et al., 2013) and 75 mg/m^2 (Markman et al., 2016), respectively. The molecular weight of camptothecin is 348.4 grams/mol (*Compound Summary - Camptothecin*, n.d.). Therefore, the MTD of camptothecin encapsulated in CRLX-101 would be 0.00004306 mol/m^2.

Equation 2:Calculations of MTD in moles of camptothecin in CRLX-101

$$\frac{15\ mg}{m^2}(MTD\ of\ CRLX101)*\frac{1\ mol}{348.352\ g}(molar\ mass\ of\ camptothecin)*\frac{g}{1000\ mg}$$
$$=0.00004306\ \frac{mol\ camptothecin}{m^2}$$

Equation 3: Calculations of MTD in moles of docetaxel in CRLX-301

$$\frac{75\ mg}{m^2}(MTD\ of\ CRLX301)\ *\frac{1\ mol}{807.879\ g}(molar\ mass\ of\ docetaxel)*\frac{g}{1000\ mg}$$
$$=0.0000928357\ \frac{mol\ docetaxel}{m^2}$$

Abraxane:

Abraxane (a successful approval by the FDA) consists of a serum albumin-bound to a paclitaxel particle. Paclitaxel (and other taxanes) function to stop mitosis by disrupting microtubule depolymerization, arresting mitotic cells in metaphase, and eventually leading to cell death (Urry et al., 2016). Human serum albumin is a protein found in blood, with its main function being the transport of hydrophobic substances (Fanali et al., 2012). It is also preferentially taken up by cancer cells. Since paclitaxel is a hydrophobic compound, binding it to albumin is an excellent way to ensure that the drug is taken up by cancer cells.

The MTD of Abraxane is 300 mg/m^2. The molecular weight of paclitaxel is 853.906 grams/mol. Therefore, the MTD of paclitaxel encapsulated in Abraxane is 0.000351326 mol/m^2.

Equation 4: Calculations of MTD in moles of Paclitaxel of Abraxane

$$\frac{300\ mg}{m^2}(MTD\ of\ abraxane) * \frac{1\ mol}{853.906\ g}(molar\ mass\ of\ paclitaxel) * \frac{g}{1000\ mg}$$
$$= 0.000351326\ \frac{mol\ paclitaxel}{m^2}$$

The above calculations show that Abraxane delivers far more therapeutic agent (paclitaxel) into the body than the other drug delivery methods. Abraxane delivers approximately 5 times the amount of therapeutic agent than BIND-014 and CRLX-301, and 10x the amount that CRLX-101 delivers. Then, considering the fact that approximately 0.7% of all the introduced therapeutic agent reaches the tumor (Wilhelm, 2016), the effective amounts reaching the tumor drop to the ranges of approximately 5 x 10^{-7} mol/m^2, whereas Abraxane delivers approximately 2.46 x 10^{-6} mol/m^2. Therefore, this could be a possible reason for failure in clinical trials.

Conclusion

Nanoparticles in cancer treatment have had successes, yet more often than not, proposed designs are based on models which do not translate well to humans. Additionally, most cancer drugs suffer from a high excretion rate and as such do not deliver a substantial amount of therapeutic agent. Such failures are exemplified by BIND Therapeutics and Cerulean Pharma. These incidents of false promise show that the pipeline of development for nanoparticles must change somehow, in order to increase the quality of healthcare received by patients seeking treatment.

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