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Review Article

A Review Article on Clinical Trials on Hybrid Drugs and Nanohybrid Technologies in Drug Development that Combat Cancer

Timothy Allen, MD, Ph.D[*1], Giridhar M.N.V, MD,MBA[1], Ghazaleh Shoja E Razavi MD[2]

[1]*Global Allied Pharmaceutical, Center for Excellence in Research & Development, USA.*

[2]*Dir. Clinical Development- Oncology and Respiratory, Global Allied Pharmaceutical, USA.*

**Corresponding author: Dr. Timothy Allen, MD, PhD, Global Allied Pharmaceutical, Center for Excellence in Research and Development, USA, Tel: 321-945-4283; Email: Timothy.Allen@gapsos.com*

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Abstract

Cancer is one of highly prevalent disease worldwide that affects different organs of the body leading to rapid and uncontrolled division of cells forming a mass of tumor cells. There are several conventional therapies available for cancer diagnosis like Xray, magnetic resonace, CT, tomography, B ultrasound, endoscopy and cancer treatment such asradiotherapy, chemotherapy, surgery. but there is growing need for a novel drug delivery system which can target only cancerous cell and not affecting healthy cells. Nanotechnology has come up with one of the drug delivery system to work at nano scale based in the area of bioengineering, medicine and pharmacology. Based on previous experience engineer are trying to evolve a new treatment system which can reduced the side effects occurring due to conventional procedures. Hybrid drug and Nanohybrid technology are the most advance technology for the effect treatment of Cancer. . Hybrid drugs are being designed to combine two anti-cancer agents so that they can act more effectively and nanodrugs are being developed to improve delivery of the therapeutic agent to the cancerous site without causing side effects to healthy cells. In this review, we discussed several in vitro research and clinical research conducted on several hybrid drugs (p63-53o and Specific and Non-genetic IAP-dependent Protein Eraser, and Hybrid 9) and nanodrugs such as pegylated liposomal doxorubicin, albumin-bound paclitaxel, and N-(-2 hydroxypropyl) methacrylamide-doxorubicin (N-(2-hydroxypropyl) methacrylamide) copolymer-Mesochlorin e6), which showed them to be effective treatment gaining importance in cancer therapeutics.

Keywords: Hybrid Drugs; Cancer; Nanocancer; Liposome Nanoparticles; Nano Hybrid Technology; Advance Chemotherapy; Nanotechnology

Abbreviations

HSPC: Hydrogenated Phosphatidylcholine;
FDA: Food And Drug Administration;
Eggpg: Egg Yolk Phosphatidylglycerol;
DSPC: 1, 2-Distearoyl-Glycero-3-Phosphocholine;
PEG: Polyethylene Glycol;

HPMA: N-(-2 Hydroxypropyl) Methacrylamide;
PLA: Poly (Lactic Acid);
PLGA: Poly(Lactic-Co-Glycolic Acid);
PAMAM: Polyamidoamine;
TNF: Tumor Necrosis Factor;
SNIPER: Specific and Non-Genetic IAP-Dependent Protein Eraser;
Ciap1: Cellular Inhibitor of Apoptosis Protein 1;
Erα: Estrogen Receptor A;
POSS: Polyhedral Oligomericsilsesquioxane;
PLD: Pegylated Liposomal Doxorubicin;
STS: Soft Tissue Sarcoma;
MBC: Metastatic Breast Cancer;
PDT: Photodynamic Therapy;
NSCLC: Non-Small-Cell Lung Cancer;
MTD: Maximum Tolerated Dose;
Nab-Paclitaxel: Nanoparticle Albumin-Bound Paclitaxel

Introduction

Cancer medically known as malignant neoplasia, is a group of diseases which involves unregulated cell growth. Malignant cells grow and divide uncontrollably, forming malignant tumors, which may spread to different parts of the body. There are over 200 different types of cancers that are known to affect human [1].

The American Cancer Society reported that total of 1,660,290 new cancer cases and 580,350 cancer deaths occurred in the U.S. in 2013. The cancer death rates decreased by 1.5% per year in women and by 1.8% per year in men. Death rates for major cancer sites (colorectal, lung, breast, and prostate) continue to decline due to recent advance in diagnosis and treatment in cancer at all stages. As per the facts provided by American cancer society inc, a decline of approximately 40% is seen in death cases for prostate cancer and 30 % for cancer related to other site like lung cancer, breast cancer and colon cancer is observed since 1991. Although gastric cancer is still an area needs more improvement. [2] As per the facts available for 1980 to 2005, only 3.6 to 4.9% decline is observed in mortality rate for both men and women, which is unaccountable [3].

Common treatments used for cancer are surgery, radiation therapy and chemotherapy. The chances of surviving the disease are affected by the location and type of the cancer and also on the extent of disease at the start of treatment [4].

Surgery: The primary method of treatment of most isolated solid cancers is surgery and may play a role in prolongation of survival. For some types of cancer this is all that is needed to eliminate the cancer [9].

Radiation therapy: It uses ionizing radiation, such as gamma-raysto either improve or cure the symptoms of cancer [5-7]. Radiation therapy is usually provided in addition to chemotherapy and surgery but may be used alone for certain cancer types, such as head and neck cancer [8].

Chemotherapy: Another method available for cancer treatment is chemotherapy which involves delivering of anti-cancer drugs that kills rapidly dividing cancer cells. It may include use of a single drug or combination of several drugs (polychemotherapy) [10].

However, there are several side effects associated with these treatment methods such as surgery, chemotherapy and radiotherapy affects normal cells in addition to cancerous cells and may lead to several other side effects and toxicities.

Surgery a common therapeutic option leads to several post-operative complications such as pain, nausea, vomiting [11-13] and non-healing wounds [14].

Several side effects of radiotherapy include hair loss, skin irritation, oral mucositis, fatigue, loss of taste and increase risk of post-operative complications [7].

The major side effect of chemotherapy is that it addition to targeting tumor cells, it also kills normal rapidly dividing cells further resulting in other side effects such as alopecia (hair loss), myelosuppression (decreased production of blood cells), and mucositis [7].

Hybrid Drugs

Cancer is a complex disease, thus it is unlikely that a single mono functional 'targeted' drug can effectively treat this disease in most advanced stage [16]. Combined drugs that have potential to impact multiple targets simultaneously can control complex disease systems, are the standard of care in cancer treatment, and are less prone to drug resistance. In order to improve the efficiency of using two-drug simultaneously, one approach involves the use of the so-called hybrid drugs. These hybrid drugs comprise the incorporation of two drugs in a single molecule that can exert dual drug action [16].

Hybrid Anticancer Drugs are new therapeutics for cancer which has potential to overcome most of the pharmacokinetic drawbacks encountered with use of conventional anticancer drugs such as doxorubicin [17].

Targeted drug delivery to cell populations of cancer sites is an active area of research today as most of the anti-cancer agents cause side effects on healthy or normal body cells that is non-cancerous cells [18].

This article will reflect on several hybrid technologies and will review clinical trials on hybrid drugs as well as hybrid technologies that are being used to develop anticancer agents. The review will focus on efficacy and benefits of hybrid drugs in combating cancer. Several hybrid drugs in use and under trials

include nanocancer drugs [19].

As we have already discussed that major side effect of chemotherapy is killing of normal cells in addition to tumor cells by chemotherapeutic agents. So, anticancer drugs have been combined with a delivery system which helps them to target the disease site, thus reduced damage to normal cells. These delivery systems have been called as hybrid drug delivery systems. Nanotechnology is a multidisciplinary field that uses principles from chemistry, engineering, physics, and biology to fabricate nanoscale devices with a size range of 1-100nmBenefits of nanotechnology are in the areas of imaging, detection, and therapy of disease. One area where nanotechnology has the potential to make a significant impact is drug delivery [28].

Several nanoscale drug delivery systems are already available in the clinical settings. Nanoscale drug delivery systems encapsulate therapeutics agents such as peptides, nucleic acids, protein-based drugs, and small molecules (hydrophilic and/or hydrophobic). Encapsulation of these drug molecules improves their stability and solubility [29]. Encapsulated drug is released in controlled from nanocarriers to maintain a drug concentration within a therapeutic window [30].

Engineering of the surface of the nanocarrier is done to increase its circulation in the blood and to enhance the biodistribution, and attaching of targeting ligands to the surface of nanocarrier can result in enhanced uptake by target tissues [31-32].

We will discuss several nanoparticle drug delivery systems that are gaining wide acceptance in cancer therapy, such as liposome nanoparticles, polymeric drug conjugate, polymeric nanoparticles, micelles, dendrimers, proteins, biological nanoparticles, inorganic nanoparticles [33-36].

Liposome Nanoparticles

Lipids form nanoparticle vesicles through the self-assembly of amphiphilic lipidsand excipients. The lipids form a bilayer based on hydrophobic interactions incontinuous parallel packing, with the hydrophilic head groups positioned towardsthe aqueous environment. Hydrophilic molecules can be encapsulated in the inneraqueous phase while hydrophobic molecules can be carried in the hydrophobicdomains of the lipid bilayer. Physicochemical properties of liposome can beprecisely changed to control surface charge, functionality, and size by simplymixing commercially available lipid molecules. This offers a significant advantageover other carriers that require much more controlled synthesis steps and additionalchemical modifications. Lipids suchasHSPC (hydrogenated phosphatidylcholinefrom soybean lecithin), EggPG (egg yolk phosphatidylglycerol) and DSPC(1,2-distearoyl-glycero-3-phosphocholine) have been approved by the U.S. Food and Drug Administration (FDA) [37].

Doxil, a pegylated liposome loaded with doxorubicinhas been used clinically to treat multiple types of cancers. Several other drugs such as campothecin, docetaxel, and bryostatin-1 has been delivered through nanosomes (small liposomes, <100 nm) [38-43].

Polymer–Drug Conjugates Nanoparticles

They are formed through side-chain grafting of drugs to polymer chains which allows themto deliver high doses of chemotherapeutic drugs. Polymer–drug conjugates are currently in phase III clinical trials. The first synthetic polymer-anticancer drug that entered clinical trials was N-(-2 hydroxypropyl) methacrylamide (HPMA)-doxorubicin (N-(2-hydroxypropyl) methacrylamide) copolymer (PK1) [34]. Polyaminoacids, are another polymer-drug conjugates grafted with drugs on the side chains that have been identified to possess high drug loading and efficacy[42]. For Example: polyglutamate-glycine-campthotecin(CT-2106) [43-44].

Polymeric Nanoparticles

They are the most effective nanocarriers for prolongeddrug delivery. Such as polyalkylcyanoacrylate-basednanoparticles releasing doxorubicin, use of poly(lactic acid)/poly(lactic-co-glycolic acid) (PLA/PLGA) and PEG block copolymer as "long-circulatingnanoparticles" [45]. Some common polymers used for nanoparticles formation include dextran, poly(lactic acid) (PLA), and chitosan [46].

Micelle Nanoparticles

Micelles may be composed of lipids or other amphiphilic molecules, such as polyamino acids or polymers, and self-assemble into small nanoparticles composed of ahydrophobic core. Hydrophobic drugs have been delivered using micelles as drug delivery carriers [47].Some of micellar formulations in clinical trials are Genexol-PM, NK105, NC-6004, NK911[48-51].

Dendrimer Nanoparticles

Dendrimers (5–10 nm) possess well-defined branchingarchitectures and surface functional groups available for further modification. They have remarkable pharmacokinetic properties and molecular monodispersity for systemic drug delivery [52]. For example: methotrexatepolyamidoamine(PAMAM) [53].

Protein Nanoparticles

Development of albumin bound drug nanoparticles (~130 nm) has recently made a big impact on protein-based drug delivery systems.Albumin-boundpaclitaxel (Abraxane, ABI-008,) has been approved by the FDAin 2005 for metastatic breast

cancer therapy, as well as in clinical trials for targeting other types of cancer [54].

Biological Nanoparticles

Biological nanoparticles such as bacteria with different sizes and shapes that encapsulate essential components of the cytoplasmas well as hydrophilic and hydrophobic molecules."Nanocell" which consists of anucleate globular bacteria (~400 nm), developed by EnGeneIC Pty Ltd is an example of biologicalnanoparticles that is being investigated for cancer therapy [37].

Inorganic Nanoparticles

Inorganic nanoparticles are metal-based and have the potential to besynthesized with near monodispersity. Intrinsic properties of inorganic nanoparticles have been explored fortherapy. Metal nanoparticles are currently under clinical trials, such asiron oxide nanoparticles coated with aminosilane(Nanotherm M01). CytImmune Sciences, Inc. have developed Aurimune (CYT-6091), tumor necrosis factor (TNF)-alpha, bound to PEG-coated gold nanoparticles (~27 nm) for solid tumortherapy [56].

Nanohybrid technologies

Now, we will discuss results of several clinical trials on hybrid drugs and nanohybrid technologies.Researchers conducted an *invitro* research on a series of novel 1,2,4-trioxane-based hybrids incorporating egonol and/or ferrocene fragments against the multidrug-resistant P-glycoprotein-over-expressing CEM/ADR5000 cells.

A remarkable cytotoxicity toward CCRF-CEM cells (IC50 of0.25, 0.07, and 0.18 μM, respectively) was shown by novel hybrids 9 (1,2,4-trioxane-ferrocene), 7 (1,2,4-trioxane-ferrocene-egonol), and 11 (artesunic acid-egonol). Hybrid 9 containing a ferrocene fragment and 1,2,4-trioxane has shown to be the most effective among the studied hybrids against the tested multidrug-resistant leukemia CEM/ADR5000 cells (IC50 of 0.57 μM) [57].

The regulation of p53 (tumor suppressor) activity differs significantly from that of p63 and p73. The tumor suppressive activity of p53 was enhanced by constructing six recombinant adenoviruses that encode hybrid proteins with three functional domains derived from either TAp63γ or p53. The role of these hybrid molecules in suppressing tumorigenesis was evaluated using *in vivo* and *in vitro* models. The hybrid named p63-530 was found to be the most potent activator of apoptosis in human cancer cells.

Researchers have developed SNIPER (Specific and Non-genetic IAP-dependent Protein ERaser), which is composed of two ligands connected by a linker, one is a ligand for a target protein and the other is cellular inhibitor of apoptosis protein 1 (cIAP1). Researchers have used tamoxifen as a ligand for estrogen receptor α (ERα) in a novel SNIPER to knockdown ERα protein. SNIPER(ER) induced degradation of ERα and inhibited expression of pS2 gene in breast cancer MCF-7 cells. Following the ERα degradation, the SNIPER(ER)-treated MCF-7 cells undergo rapid cell death[59]. Kawamoto and his colleagues conducted *invivo* and *invitro* research on the newly designed HER2-lytic hybrid peptide that lead to cancer cell death via membrane lysis.High cytotoxicity of HER2-lytic hybrid peptide was observed against breast and cancer cell lines that are resistant to lapatinib and/or trastuzumab*in vivo* and *in vitro*[60]. Polyhedral OligomericSilsesquioxane (POSS)-F68 hybrid vesicles (average diameter of 700 nm) are another hybrid drug delivery systems that have been used for making doxorubicin and folic acid loaded vesicles. POSS-F68 vesicles in combination with a chemotherapeutic and folic acid have potential for targeted intracellular anti-cancer drug delivery. Flow cytometric and confocal microscopic studies on the endocytosis of the vesicles by HOS and HeLa cells prove that a noncovalent entrapment of excess folic acid in the vesicles through H-bonding can significantly enhance the uptake [61]. Fig 1.Researchers conducted a clinical trial on twenty-eight patients to evaluate the impact of pegylated liposomal doxorubicin (PLD), a formulation with pharmacokinetic differences with respect to doxorubicin (DXR), onquality of life of patients with advanced soft tissue sarcoma (STS) pretreated with DXR. Patients were given 35 mg/2 of PLD every 3 weeks. The study observed Grade 3 toxicity: stomatitis (4%), palmar-plantar erythrodysesthesia (19% of patients), or cutaneous (4%). Progression-free rate at 3 and 6 months was 48% and 22%, respectively, median overall survival 8.7 months and median progression-free survival 5.8 months. Measurement of patient's quality of life with EORTC QLQ-C30 showed that the therapy didn't worsen the quality [62].

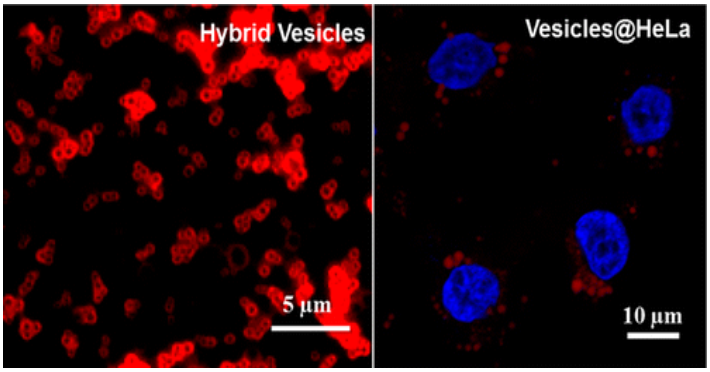

Figure 1. Polyhedral OligomericSilsesquioxane (POSS)-F68 hybrid.

A phase III randomized clinical trial was conducted on 509 women's with metastatic breast cancer (MBC) to compare effi-

cacy of PLD and doxorubicin in treatment. Subjects receivedeither doxorubicin 60 mg/m2 (every 3 weeks) or PLD 50 mg/m2 (every 4 weeks). Efficacyof PLD and doxorubicin in first line therapy for MBC was comparable, with significantly reduced cardiotoxicity, vomiting, neutropenia, alopecia andnausea[63]. Another study on human ovarian OVCAR-3 carcinoma xenografted in female athymic mice was conducted to assess the effectiveness of HPMA-doxorubicin (N-(2-hydroxypropyl) methacrylamide) copolymer-mesochlorin e6 and adriamycin Conjugates in treating ovarian cancer when used in combination with other anticancer therapies including chemotherapy and photodynamic therapy (PDT). OVCAR-3 tumors were suppressed with 13.4 mg/kg (1.5 mg/kg of Mce6 equivalent) dose of HPMA copolymer-Mce6 conjugate (PDTMC) and light doses of 110 J/cm2 at 12 and 18h [64].

Phase I Clinical trial of HPMA copolymer–anticancer conjugates, HPMA copolymer–Gly-Phe-Leu-Gly-doxorubicin, with increasing doses up to a maximum-tolerated dose of 320 mg per m2 in chemotherapy-resistant patients showed cardiotoxicity, renal elimination (50–75% over the first 24 h), prolonged plasma circulation(t1/2a = 1.8 h), an absence of liver accumulation[65-66] and partial responses in patients with breast cancer and non-small-cell lung cancer(NSCLC) were observed in phase II trials [67]. These studies confirmed that HPMA copolymer could be used to deliver more than 20 g per m2 of dose without polymer-related immunogenicity and toxicity. Genexol-PM, nontargetedpolymeric micellar, was approved as a first-line therapy for NSCL cancer and metastatic breast in Korea in 2006. Genexol-PM is formed of block copolymer PDLLA (1.75 kDa)–mPEG (2 kDa) micelles (size of ~60 nm) loaded with paclitaxel (~15% (w/w)). This preparation is currently under phase II trial for metastatic pancreatic cancer therapy in the U.S. It showed that maximum tolerated dose(MTD) of Genexol-PM (60 mg kg-1) is three folds higher than that of Taxol (20 mg kg-1).

In Korea, clinical phase II trial evaluated Genexol-PM as a co-therapy with cisplatin for advanced NSCL in contrast to a single agent therapy. The study resulted in stable disease status in more than 30 % of the patients and increased survival of one year in 60 percent patients [68].An in vitro study on use of the anticancer drug-methotrexate-encapsulated with PAMAM dendrimer conjugated chitosan nanoparticles was conducted. The cell viability assay showed that CS-PAMAM may have potential role for the water-insoluble drug delivery because of its low cytotoxicity on cells [69].

Gupta and Hatoum conducted a phase III trial to assess the effects of weekly treatment of nanoparticle albumin-bound paclitaxel ([nab-paclitaxel] ABRAXANE® ABI-007) in combination with carboplatin versus solvent-bound (sb)-paclitaxel in combination with carboplatin given every 3 weeks for first line treatment of non-small-cell lung cancer (NSCLC). The study showed that weekly treatment with nab-paclitaxel resulted in increased survival of NSCLC patients [70]. Fig 2.

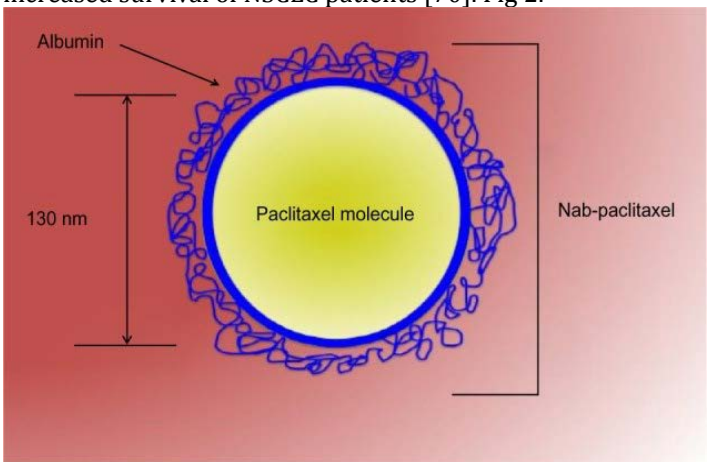

Figure 2. Graphic representation of nanoparticle albumin-bound paclitaxel (nab-paclitaxel).

Discussion

The enhancement of the tumor-targeting efficacy of chemotherapeutic agents is a key issue in management. To overcome this challenge, researchers have developed hybrid drugs and various hybrid technologies (nanohybrid technologies). In this article, we discussed several hybrid drugs including 1,2,4-trioxane-based hybrids incorporating egonol and/or ferrocene, p63-530 SNIPER (Specific and Non-genetic IAP-dependent Protein ERaser) with tamoxifenas a ligand. All these hybrid drugs are currently under in vitro and in vivo studies and have proved to have higher potential for targeting different forms of cancer. Clinical trials in humans are to be conducted to assess the efficacy and safety of these hybrid drugs in humans.

Further, several nanoscale-based hybrid drugs have been developed of which some are already under clinical use, while others are under different phases of clinical trials. These nanohybrid drugs have been designed to improve the drug delivery system for chemotherapeutics. This article reviewed clinical as well as in vitro studies of several nanohybrid technologies such as PLD,nab-paclitaxelandGenexol-PM. All studies showed nanohybrids to be superior method for drug delivery as they enhances efficacy of drug at the targeted site as well reduced side effects to normal body cells.

Conclusion

Hybrid drugs are gaining high acceptance as a treatment option for various forms of cancer. Although, these hybrid drugs have been well studied both in vitro and in vivo (animals) but may not produce desired therapeutic effects in humans. So, clinical trials in humans are needed to be conducted in order to assess their therapeutic effects, safety as well as their impact

on quality of life of humans.

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