Review Article

Emerging chemotherapy agents in lung cancer: nanoparticle therapeutics for non-small cell lung cancer

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Abstract: The introduction of nanotechnology has brought about major progress in modern medicine. Nanotechnology involves the use of nanosized materials, or those measured at the level of 1 nanometer, or one-billionth of a meter. In the treatment of cancer, nanotechnology has been used to deliver cytotoxic agents with higher drug content, improved targeting to tumor sites, and decreased accumulation into non-tumor organs. These nanoparticle chemotherapy agents have superior efficacy and less toxicity compared to standard chemotherapy, and have been studied in various solid and hematologic malignancies. A number of nanoparticle chemotherapy drugs have been developed in recent years, a number of which have had success in lung cancer as well as other tumor sites. The first of these to be approved for non-small cell lung cancer (NSCLC) is Abraxane, or albumin-bound paclitaxel. In this review, we discuss the rationale and the approach for the use of nanoparticle technology in chemotherapy, as well as the unique advantages that these drugs provide. Afterwards, we will focus on emerging nanoparticle agents that have demonstrated promising clinical data for the treatment of advanced NSCLC.

Keywords: Chemotherapy; drug delivery; lung cancer; nanoparticles; nanotechnology

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Introduction

Since the late 1990s, platinum-based doublet chemotherapy has been the standard of care for treating non-small cell lung cancer (NSCLC) patients without actionable mutations. ECOG 15-94 compared four regimens (cisplatin/gemcitabine, cisplatin/docetaxel, cisplatin/paclitaxel and carboplatin/paclitaxel) among more than 1,200 patients and found equal efficacy, with all four regimens leading to survival rates of 33% at 1 year and 11% at 2 years in advanced NSCLC (stage IIIB-IV) (1). However, these regimens have significant toxicity, and their benefit is limited to patients with good performance status (ECOG 0-1). Patients who are elderly or unfit (ECOG ≥2) have shorter survival and more chemotherapy-related toxicity (2). Often times, these patients are not offered 1st line systemic chemotherapy due to the unfavorable risk-benefit ratio. Another limitation to platinum doublet chemotherapy is its limited efficacy in refractory disease. While targeted therapy [EGFR (3), ALK (4) inhibitors], and immunotherapy [anti-CTLA-4 (5), anti-PD-1 (6,7)], have led to improved survival and response rates in NSCLC, there remain a significant proportion of patients who do not benefit from these strategies, or whom cannot tolerate them.

To meet these needs, nanoparticle delivery systems present a novel approach for delivering cytotoxic drugs in the treatment of NSCLC, both with higher efficacy and lower toxicity. Abraxane, or albumin-bound nanoparticle paclitaxel, is the first nanoparticle therapy to be FDA-approved for use in NSCLC, based on its improved

Table 1 Overview of nanoparticle-based therapies used in lung cancer

Drug delivery systems	Agent	Drug (% of compound w/w)	Size	Composition	Surface modifications	Targeting ligands	Target receptor
Liposomal nanoparticles	Lipoplatin (10)	Cisplatin (8.9%)	110 nm	DPPG, SPC-3, cholesterol, $mPEG_{2000}$-DSPE	PEG	None	None
	Doxil (11)/Caelyx	Doxorubicin (12.5%)	85 nm	HSPC, cholesterol	DSPE-PEG	None	None
Polymeric nanoparticles	Abraxane (12)	Paclitaxel (10%)	130 nm	Albumin polymer	None	None	None
	BIND-014 (13)	Docetaxel (10%)	100 nm	PLA-PEG polymer	PEG	ACUPA	PSMA
Polymeric micelles	Genexol-PM (14)	Paclitaxel (20%)	20-50 nm	mPEG-PDLLA copolymer	mPEG	None	None
	NC-6004 (15) (Nanoplatin)	Cisplatin (39%)	28 nm	PEG-P(Glu) copolymer	PEG	None	None

w/w, by weight; nm, nanometer; DPPG, dipalmitoyl phosphatidyl glycerol; SPC-3, soy phosphatidyl choline; $mPEG^{2000}$-DSPE, methoxy-polyethylene glycol-distearoyl phosphatidylethanolamine; PEG, polyethylene glycol; HSPC, hydrogenated soy phosphatidylcholine; DSPE, distearoylphosphatidylethanolamine; PLA, polylactic acid; ACUPA, S,S-2-[3-[5-amino-1-carboxypentyl]-ureido]-pentanedioic acid; mPEG, monomethoxy polyethylene glycol; PDLLA, poly (D,L-lactic acid; P(Glu), polyglutamate; PSMA, prostate specific membrane antigen.

Table 2 Unique advantages of nanoparticle therapuetics

Large "payload"
Multivalent ligand targeting
Combination therapeutics
Bypass of multidrug resistance mechanisms

outcomes and decreased adverse events (8,9). This drug is likely just the first of many, as nanotechnology drug delivery continues to be refined and further utilized. In this review, we discuss emerging nanoparticle therapies for NSCLC. We will first provide an overview of nanoparticle therapies, then provide specific examples of novel agents which have produced promising data (*Table 1*).

Nanoparticle therapies

The advent of nanotechnology has brought with it the potential for nanoparticle therapeutics in cancer therapy. Nanoparticles, or nanomaterials, by definition measure 1-100 nm in at least one dimension (16,17). It should be noted that nanoparticle systems may be used for various medical purposes [e.g., imaging (18), immune adjuvants (19)] in addition to therapeutics, and while these agents may be larger, up to 200-500 nm in size, this does not necessarily impact their functionality or detract from their size-dependent properties. Nanoparticles may be engineered as the drug delivery carrier, or the drug itself can be engineered at a nanoscale, in which case the drug serves as its own "carrier" (20-22). Nanomaterials used in cancer nanotherapeutics include lipids, polymers, dendrimers, organometallic and carbon based materials (23).

Nanotechnology drug delivery systems offer several advantages compared to standard chemotherapy. Due to their size dependent properties and additional modifications, nanoparticle drugs can be designed to achieve prolonged circulation times, greater stability, improved intratumoral accumulation and concentration, and decreased toxicity to normal tissues. As such these nanoparticle therapeutics represent more effective therapies with diminished side effects.

Nanoparticles have four particularly unique characteristics (*Table 2*), thanks to their size and relatively large surface area (up to 1,000 m^2/g): (I) large "payload", or the ability to carry large amounts of drug; (II) multivalent ligand binding, as higher density of targeting moieties leads to higher affinity binding; (III) combination therapeutics, as their large surface to mass ratio can accommodate multiple drugs simultaneously; and (IV) bypass of multidrug resistance mechanisms involving cell surface protein pumps, e.g., P-glycoprotein (24).

Physical characteristics of nanoparticles

The ideal nanoparticle drug delivery systems range in

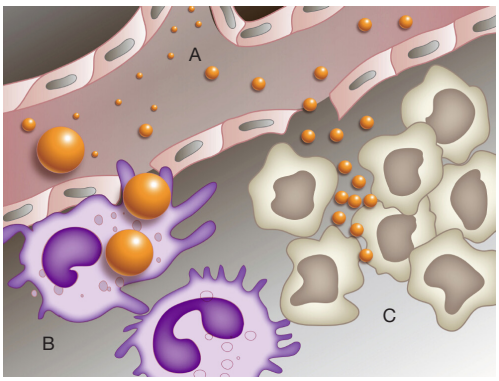

Figure 1 Nanoparticle chemotherapeutic targeting is a size dependent process. Ideal nanoparticle drug delivery systems should be designed to range in size from 10-100 nm in diameter. (A) Nanoparticles smaller than 10 nm will be removed by single-pass renal clearance; (B) nanoparticles larger than 100 nm will be captured by macrophages or Kupffer cells; (C) nanoparticles sized 10-100 nm penetrate leaky gap junctions between tumor endothelial cells and accumulate into tumor sites.

size from 10-100 nm (*Figure 1*). Nanoparticles larger than 10 nm and greater than 50 kDa will avoid leakage into capillaries and removal by single-pass renal clearance (25,26). Nanoparticles smaller than 100 nm will escape capture by macrophages in the reticuloendothelial system (RES) (27), where sinusoids in the spleen and the fenestra of Kupffer cells in the liver range from 150-200 nm (28). Furthermore, tumor blood vessels possess wide gap junctions measuring 100-600 nm in size, so nanoparticles smaller than 100 nm will optimally penetrate and accumulate into tumor tissues (29-31).

Nanoparticle surfaces can also be modified to optimize their efficacy and targeting. Nanoparticles with hydrophobic surfaces are prone to macrophage capture by the RES (32,33). Thus, modifications to create more hydrophilic surfaces will help evade removal by the RES. Polyethylene glycol (PEG) is the most widely used modification to render nanoparticles more hydrophilic (32). PEGylation of nanoparticle surfaces prevents opsonization, blocking RES capture, and leading to improved circulation time and tumor site accumulation. Alternatively, nanoparticles can also be formed using block copolymers with both hydrophilic and hydrophobic domains (34). Neutral or negatively charged nanoparticle surfaces are also preferred, because positively charged nanoparticles are more readily taken up by the RES (35).

The shape and flexibility of nanoparticles can also be adjusted to improve circulating time. Spherical shaped nanoparticles are more likely to maintain streamlined movement through a vessel (36,37). Soft, flexible nanoparticles are less susceptible to macrophage capture (38,39).

Passive targeting (EPR)

Passive targeting is a size dependent process that capitalizes both on the size and surface characteristics of nanoparticles, as well as the unique features of tumor vessel pathophysiology. Nanoparticles sized 10-100 nm and with the appropriate surface characteristics will evade capture by the RES. As a result, they are retained in the circulation for longer periods and have a higher likelihood of reaching tumor sites. Tumor tissues, meanwhile, are characterized by rapid cell proliferation, active neovascularization and an imbalance of proangiogenic growth factors. Vascular endothelial growth factor (VEGF), bradykinin (40), prostaglandins (40), nitric oxide (40), peroxynitrite ($ONOO^-$), and matrix metalloproteinases (41), all increase the vascular permeability of tumors (42). The end result is an irregular, highly distorted vasculature with wide, leaky gap junctions that are prone to extravasation by nanoparticles smaller than 100 nm in size and with a molecular weight above 50 kDa (43). Because these tumor tissues have poor lymphatic drainage, nanoparticles will be retained in these intratumoral sites for prolonged periods (29,44). This combined effect, whereby nanoparticles exploit the leaky vasculature and impaired lymphatic drainage of tumors, is known as the enhanced permeability and retention effect (EPR) (29). The EPR effect produces higher intratumoral drug concentrations and simultaneously decreased systemic exposure to normal organs; this is a unique advantage of nanoparticle delivery systems and critical to their success in cancer therapy.

Another strategy to improve passive targeting of nanoparticles is via pH-sensitive release (45,46), whereby the cytotoxic drug payload is only delivered upon reaching specific conditions found in the tumor microenvironment. For example, pH-sensitive liposomes are designed to remain stable at physiologic pH, but will degrade and release their active agent at a lower pH. Because tumor cells utilize glycolysis for additional energy production (47), they have an acidic environment, and pH-sensitive liposomes will only activate at this specific location (46).

Active targeting

While passive targeting localizes nanoparticle drugs to

intratumoral sites via the EPR effect, it does not ensure intracellular uptake. Active targeting is a strategy to further improve nanoparticle targeting within the cancer cells themselves. Nanoparticles are modified with specific, surface-bound ligands which allow the drug to home with high affinity to corresponding receptors expressed on the cancer cell. Ligand binding to the cancer cell surface receptor triggers receptor-mediated endocytosis, which internalizes the drug deep into the cell. This is an important strategy, because the ability to bypass membrane efflux pumps may allow nanoparticles to overcome drug resistance.

Various moieties, such as peptides, aptamers, proteins, and antibodies, can be added to the surface of nanoparticles as ligands to facilitate conjugation with cancer cell receptors. Examples of cancer cell receptors that have been studied as targets for nanoparticles in lung cancer include the folate receptor (48), EGFR (49,50), transferrin receptor (51), epithelial cell adhesion molecules (EpCAM) (52), interleukin-4 receptor (53), fibroblast activation protein alpha (FAPα) (54), and prostate specific membrane antigen (PSMA) (13).

Preclinical studies suggest that active targeting improves antitumor efficacy as a result of enhanced cellular internalization of cytotoxic agents, rather than increased tumor accumulation (55). This strategy allows not only the further specific targeting of nanoparticle therapeutics, but also decreased toxicity to non-tumor tissue sites. With improved tumor targeting, there will be less drug leakage, less localization of drug at normal tissues, and less degradation or clearance of drug. At the clinical level, this should result in less toxicity for the patient, and allow for higher therapeutic doses to be tolerated.

Overcoming drug resistance

Multidrug resistance in cancer cells is commonly due to over expression of broad spectrum drug efflux pumps in the cellular membrane which non-specifically transport drugs out of the cell, and thereby lower intracellular drug concentrations (56). This leads to tumor cells with resistance to multiple drugs via the same mechanism.

The most prominent family of drug efflux pumps is the ATP-binding cassette (ABC) transporter family of efflux pumps. Among these, the first described drug efflux pump was P-glycoprotein (Pgp) (57,58), the end product of the ABCB1 (or MDR1) gene (59). Pgp is a transporter of cationic lipophilic substances, and may confer resistance to multiple classes of anticancer drugs, including anthracyclines (60), vinca alkaloids (61,62), camptothecins (63), taxanes (62), and epothilones (64). Studies in both small cell and NSCLC have shown increased MDR1 expression in up to 15-50% of tumor samples (65,66).

The multidrug-resistance associated protein (MRP1, or ABCC1) gene codes for a similar ABC transporter that is also associated with multi-drug resistance (67). MRP1 is a transporter of organic ions associated with resistance to anthracyclines (67,68), antimetabolites (69), vinca alkaloids (67,70), topoisomerase inhibitors (71), and alkylating agents (72). MRP1 is ubiquitously expressed in normal lung tissues; in NSCLC, MRP1 expression was found in 100% of samples, with 30% of samples showing increased MRP1 expression (65,73).

Unlike low molecular weight drugs less than 1 nm in diameter, nanoparticles are 1-2 magnitude larger, and thus more likely to undergo intercellular uptake via endocytosis. These drugs are taken up via endo-lysosomal trafficking, into lysosomes, and are taken deep into cells, beyond the reach of drug efflux pumps. In doing so, these nanomedicines may potentially overcome multidrug resistance due to membrane pumps in cancer cells (74). The combined use of multiple drugs within a single nanoparticle may also provide another means for overcoming multidrug resistance going forward (75,76). Combination nanoparticle therapy can act on multiple mechanisms leading to synergism and lesser toxicity through decreased doses compared to single drug regimens (76).

Nanoparticle drug delivery systems

Various nanomaterials have been utilized in cancer therapeutics, including: lipids, polymers, viruses, carbon nanotubes and organometallic compounds. For the purposes of this review, we will only describe liposomes, polymeric nanoparticles and polymeric micelle based delivery systems. Other nanomaterial delivery systems are described elsewhere and beyond the scope of this review.

Liposomes

Lipid-based drug delivery systems, also known as liposomes, are closed spherical structures where amphiphilic phospholipids and cholesterol form one or more lipid bilayers surrounding an aqueous core (77). This liposomal structure allows storage of hydrophilic drugs within the aqueous core, or for hydrophobic drugs to be associated within the lipid bilayers. By improving the solubility of cytotoxic agents, liposomes extend drug circulation times

and increase the chance of intratumoral uptake. Cytotoxic agents designed with liposomal formulations include anthracyclines (78-80), platinums (81), camptothecins (82), vinca alkaloids (83), and antimetabolites (84-86).

Doxil

Stealth™ PEGylated liposomal doxorubicin, also known as Doxil (US), or Caelyx (EU), was among the first approved nanoparticle chemotherapies, with FDA indications for ovarian cancer, AIDS-related Kaposi sarcoma and multiple myeloma. Doxil has been shown to have significantly less cardiotoxicity compared to standard doxorubicin (87-89). A phase I study demonstrated Doxil's activity as a single agent in platinum pretreated advanced or metastatic NSCLC (78); among 17 patients, there was 1 PR (5.8%) and 5 SD (29.4%), with median TTP 9.5 weeks and median survival 18.6 weeks. Because of its relatively low toxicity, Doxil 20 mg/m^2 IV was combined in a triplet regimen with docetaxel 50 mg/m^2 IV and gemcitabine 1,000 mg/m^2 IV on a 2 week cycle, for 18 patients with treatment-naïve, advanced NSCLC (17 stage IV, 1 stage III); this triplet regimen resulted in 1 CR (5%) and 6 CR/PR (33%) (90). Patients received supportive growth factors and amifostine to help reduce toxicity; there were no cases of grade III-IV toxicity.

Doxil has been studied as a radiosensitizing agent for definitive therapy of NSCLC. In a phase I dose escalation study among 15 NSCLC patients, an MTD of Doxil 25 mg/m^2 every 2 weeks for three cycles concurrently with conventional fractionated radiotherapy resulted in a CR rate of 21% (79). In a subsequent Phase I/II dose escalation study among 15 patients with stage IIIB NSCLC, the combination of Doxil 25 mg/m^2 IV every 2 weeks with docetaxel 30 mg/m^2 IV weekly during conventional fractionated radiotherapy (total 64 Gy) achieved 6 CR (40%) and 13 CR + PR (87%) (91). Supportive amifostine was administered to all patients; toxicity included grade I neutropenia in five patients (20%), grade II anemia in three patients (12%), and grade III esophagitis in nine patients (36%). The combination of Doxil with cisplatin concurrently with conventional radiation was studied in a phase I of 18 patients (9 squamous cell lung cancer, 9 squamous cell head and neck). Among all patients, there were 6 CR (33%) and 10 PR (55%) (92). A fourth study combined Doxil 20 mg/m^2 every 2 weeks for three cycles with vinorelbine during hypofractionated accelerated radiotherapy (15 fractions of 3.5 Gy over 4 consecutive weeks, with 1 week split after the 10th fraction, for a total of 65.6 Gy). All patients received supportive growth factors and amifostine. Among 14 patients, there were 9 PR (64.2%), 3 with minimal response (21.4%), and 2 SD (14.3%) (93).

Doxil has been assessed as salvage therapy for small cell lung cancer. In a Phase II study of Doxil 50 mg/m^2 IV every 4 weeks among 14 patients with recurrent small cell lung cancer, there were 3 SD (21.4%), but no PR/CR (94). Doxil 30 mg/m^2 was subsequently combined with vincristine 1.2 mg/m^2 and cyclophosphamide 750 mg/m^2, every 3 weeks among 30 patients with recurrent SCLC, producing 3 PR (10%) and 15 SD (50%) (95). A Phase II study treated 26 patients with relapsed SCLC using Doxil 15 mg/m^2 and irinotecan 125 mg/m^2 every 2 weeks, resulting in 4 PR (12.9%) and 2 SD (6.5%) (80).

MM-398

Nanoliposomal irinotecan, also known as PEP02, or MM-398, is a PEGylated liposomal formulation of irinotecan designed to offer higher drug load and stability, as compared to standard irinotecan. This formulation was able to carry a drug load of 109,000 irinotecan molecules per nanoparticle, nearly 10-20 times that of other liposomal formulations (82). *In vivo* studies showed that MM-398 achieved prolonged circulation compared to standard irinotecan, with 23.2% of injected dose of MM-398 present at 24 hours, versus only 2% of injected dose of standard irinotecan remaining at 30 minutes (82). In preclinical models, MM-398 showed both higher antitumor efficacy and lower toxicity compared to standard irinotecan in models of squamous cell lung cancer (96) and small cell lung cancer (96). In a Phase I dose finding study of 11 patients (including 1 NSCLC), a MTD of 120 mg/m^2 IV on Day 1 of a 3 week cycle resulted in 2 PR and 3 SD among ten patients evaluable for response, for a disease control rate of 50% (97). Unfortunately, the one NSCLC patient included in this study was removed from the study after prolonged treatment interruption (due to catheter-based infection). MM-398 was well tolerated with the most common hematologic toxicity being grade I/II anemia and neutropenia, and the most common non-hematologic toxicity being grade I/II diarrhea, nausea and alopecia. There was only one episode of grade III catheter-related infection at the MTD of 120 mg/m^2 (97).

Lipoplatin

PEGylated liposomal cisplatin, or Lipoplatin™, was

designed by Regulon, Inc. Mountain View, CA, USA and has been investigated in multiple NSCLC studies in Europe. Lipoplatin measures 110 nm in size, and consists of a lipid shell [containing dipalmitoyl phosphatidyl glycerol (DPPG), soy phosphatidyl choline (SPC-3), cholesterol and methoxy-polyethylene glycol-distearoyl phosphatidylethanolamine ($mPEG^{2000}$-DSPE)], and a cisplatin-containing core (10). The Lipoplatin™ formulation is 8.9% cisplatin and 91.1% lipid by weight.

Preclinical studies demonstrated that Lipoplatin™ has antitumor efficacy (98), with up to 50 times higher intratumoral concentrations compared to normal tissues (99), and less renal toxicity compared to standard cisplatin (100). A mouse model study of NSCLC showed that Lipoplatin™ had superior cytotoxicity in malignant cells but lower toxicity in normal cells, compared to cisplatin (101). This study also found a direct correlation between lipoplatin resistance and excision repair cross-complementing 1 (ERCC1) and lung resistance protein (LRP) expression (101). These two markers are known predictors of response to cisplatin (102-105), and may have similar utility for Lipoplatin™. DNA mismatch repair (MMR) status has also been identified as a predictor of response to lipoplatin, with MLH1-deficient cell lines showing *in vitro* resistance to lipoplatin (106).

A phase I study of 2nd-line Lipoplatin™ with gemcitabine in 13 patients with platinum pretreated, advanced NSCLC found a MTD of Lipoplatin™ 120 mg/m^2 (107). The overall disease control rate was 23% (three patients), with median OS 29 weeks (range, 4-59 weeks) and median TTP 12 weeks (range, 3-36 weeks). The combination was well tolerated with grade III or higher toxicity (nausea/vomiting, flu-like syndrome) only occurring at dose level 4 (130 mg/m^2). A subsequent phase II study of 88 patients with advanced NSCLC compared Lipoplatin™ 120 mg/m^2 IV on Days 1, 8 + gemcitabine 1,000 mg/m^2 IV on Days 1, 8 of a 3 week cycle (n=47) versus cisplatin 100 mg/m^2 IV on Day 1 + gemcitabine 1,000 mg/m^2 IV on Days 1, 8 of a 3 week cycle (n=44) (108). The ORR for Lipoplatin™ and cisplatin were not statistically different (31.7% *vs.* 25.6%). Of note, the lipoplatin regimen achieved significantly better responses among adenocarcinoma histology subtypes (16.7% PD), compared to squamous histology (46.1% PD). There was less toxicity with Lipoplatin™, particularly less nephrotoxicity (14.6% *vs.* 25% grades I-IV).

A phase III multicenter study of chemotherapy-naïve, inoperable NSCLC compared Lipoplatin™ 200 mg/m^2 IV on Day 1 + paclitaxel 135 mg/m^2 IV on Day 1 of a 2 week cycle (n=102) versus cisplatin 75 mg/m^2 IV on Day 1 + paclitaxel 135 mg/m^2 IV on Day 1 of a 2 week cycle (n=100) (109). Grade I-IV nephrotoxicity was significantly lower for Lipoplatin™ (6.1% *vs.* 40%, P<0.001), as were grade I-IV neutropenia (33.3% *vs.* 45.2%, P=0.017) and grade I-IV nausea/vomiting (32.5% *vs.* 45.2%, P=0.042). Median OS (9 *vs.* 10 months) and TTP (6.5 *vs.* 6 months) were not statistically significantly different. Overall response rates were not statistically significant between the two arms. However, non-squamous histologies showed a better response rate (59.5% *vs.* 42.5%) and median survival (10 *vs.* 8 months) after 18 months, with double the number of surviving patients (110).

Lipoplatin™ has been studied as monotherapy in NSCLC, at a dose of 200 mg/m^2 IV Days 1, 2 of a 2 week cycle (111). Among 21 patients (19 with ≥1 prior chemotherapy), there were 38.1% PR and 42.9% SD. Toxicity included two patients (9.5%) with grade I myelotoxicity, four patients (19.1%) with grade I nausea/vomiting and no nephrotoxicity.

A study was performed to assess the impact of Lipoplatin™ on renal insufficiency (112). A total of 40 patients with solid tumors (including 16 NSCLC) who had median serum creatinine 2.4 mg/dL (range, 1.6-3.5 mg/dL) were treated with Lipoplatin™ 150-200 mg/m^2 IV Day 1 and gemcitabine 1,000 mg/m^2 IV Day 1 on a 2 week cycle. Although grade I-II myelotoxicity occurred (attributed to gemcitabine), there were no patients with increased serum creatinine, suggesting that patients with renal insufficiency and NSCLC may be considered eligible for treatment with Lipoplatin™.

Polymeric nanoparticles

Polymer nanoparticle drug delivery systems, are solid, colloidal systems composed of a polymer matrix to which a cytotoxic drug is either covalently attached, dissolved, encapsulated or entrapped within. Polymer nanoparticles may be engineered either using natural polymers, such as albumin, chitosan and heparin, or using synthetic polymers, such as polyethylene glycol (PEG), poly-L-glutamic acid (PGA), polylactic acid (PLA), poly(D,L-lactide-co-glycolic) acid (PLGA), and N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA). One advantage to the use of polymeric nanoparticles is the ability for "controlled release", whereby the rate of biodegradation and drug diffusion through the polymer matrix can be tuned to achieve controlled release kinetics, with release durations ranging from minutes up to

weeks. Conjugation of PLGA to doxorubicin nanoparticles, for example, increased drug release from 5 days for unconjugated doxorubicin up to 25 days for conjugated PLGA-doxorubicin (113). Polymer nanoparticle formulations have been designed for several cytotoxic drugs, including taxanes (8,13,114), camptothecin (115), anthracyclines (116), and topoisomerase II inhibitors (117).

Abraxane

Albumin-bound nanoparticle paclitaxel, also known as nab-paclitaxel, or Abraxane, is FDA approved for 1st line therapy of advanced/metastatic NSCLC, as well as metastatic breast cancer and metastatic pancreatic cancer. In preclinical models, nab-paclitaxel demonstrated higher mean maximum blood concentration, higher intratumoral concentration, greater transport across endothelial cell layers, and higher antitumor activity, when compared to solvent based paclitaxel (118). This was corroborated in human pharmacokinetic studies, which showed higher systemic exposure to free paclitaxel in patients receiving nab-paclitaxel versus those receiving solvent-based paclitaxel (114). A phase III study comparing nab-paclitaxel and carboplatin versus standard solvent based paclitaxel and carboplatin as 1st line therapy for advanced or metastatic NSCLC, found improved antitumor activity and tolerability, leading to FDA approval as 1st line therapy in this setting (8). Patients treated with nab-paclitaxel had significantly less sensory neuropathy, neutropenia, arthralgia and myalgia compared to those receiving solvent based paclitaxel. Subgroup analysis demonstrated that elderly patients (70 years and older) treated with nab-paclitaxel had improved median OS (19.9 *vs.* 10.4 months, P=0.009) (119).

BIND-014

BIND-014 (BIND Therapeutics, Inc.) is a PEG-PGLA copolymer nanoparticle containing docetaxel that is targeted against PSMA. PSMA is a prostate epithelial cell surface membrane glycoprotein found on the surface of both primary prostate tumor cells and metastatic prostate cancer cells, as well as the neovasculature of other non-prostate solid tumors (120-122). In one study, 5 out of 5 (100%) NSCLC tumor samples showed overexpression of PSMA (120). BIND-014 features an S,S-2-[3-[5-amino-1-carboxypentyl]-ureido]-pentanedioic acid (ACUPA) moiety, which functions as a PSMA substrate analog inhibitor to target PSMA on target cancer cells (13).

In mouse models, BIND-014 showed enhanced tumor accumulation at 12 hours and prolonged tumor growth suppression compared to solvent-based docetaxel (13). Additional pre-clinical and clinical PK studies in both mice and monkeys have shown that BIND-014 achieves higher Cmax and AUC with reduced drug clearance and volume of distribution compared to solvent-based docetaxel (123).

A phase I study of 5 different solid tumors (prostate, cervical, NSCLC, breast and hepatobiliary) showed immunohistochemical detection of PSMA in prostate epithelium and the neovasculature of cervical, anal, NSCLC, and hepatobiliary tumors (124). All patients experienced some objective response to BIND-014 (CR, PR, or SD). A phase I safety and dose-finding study of 30 patients with solid tumors (NSCLC, 6; hepatobiliary, 5; head and neck, 3; prostate, 2; and other solid tumors, 14), resulted in 3 PR (NSCLC, cervical and hepatobiliary), as well as 5 SD (prostate, pancreas, hepatobiliary, head and neck, and anal) (125). BIND-014 was shown to have a dose-linear PK profile with prolonged circulation compared to solvent based docetaxel. The MTD was 60 mg/m^2 IV on Day 1 of a 3 week cycle. A separate phase I safety and tolerability study was performed to assess BIND-014 on a weekly dosing schedule (126). A total of 27 patients were evaluable, including three NSCLC. PK studies again showed dose-linear PK and prolonged circulation. There were two confirmed PR (breast, esophagus), and 4 SD >12 weeks (including 1 NSCLC). The MTD was 40 mg/m^2 on Days 1, 8, and 15 of a 4-week cycle, resulting in a 50% increase in dose exposure over 28 days compared to 3 week cycle dosing.

A subsequent phase II study treated 40 patients with stage III/IV NSCLC with known genomic status (EGFR, ALK or KRAS), using BIND-014 60 mg/m^2 on Day 1 of a 3-week cycle, with ORR as the primary endpoint (127). Among the 40 patients enrolled, a median of 3 doses was administered (range, 1-12). Out of 33 patients evaluable for response, there were 5 (15%) PR and 12 (36%) SD lasting ≥12 weeks. Among 8 patients with KRAS mutations, 2 (25%) had PR and 3 (38%) had SD ≥12 weeks, for a total disease control rate of 63% among KRAS mutants. Grade III/IV hematologic toxicities included anemia (8%) and lymphocytopenia (5%), while grade III/IV non-hematologic toxicity included fatigue (13%), dehydration (10%), peripheral neuropathy (3%), dyspnea (3%), and hypoxia (3%).

There are currently two phase II involving BIND-014 in NSCLC. The first is a phase II to assess safety and efficacy as second-line therapy in NSCLC patients who failed one

prior platinum-based regimen for advanced or metastatic disease. The primary outcome will be number of patients with either CR or PR, and the secondary outcome number of patients with adverse events. A second phase II study will assess BIND-014 as second-line therapy for NSCLC patients with KRAS mutations or squamous cell histology. The primary outcome will be disease control rate, and the secondary outcomes will include PFS, OS, duration of response, time to response, and safety and tolerability.

Polymeric micelles

Polymeric micelles utilize self-assembling amphiphilic block copolymers to form a hydrophilic outer shell region that surrounds a hydrophobic core (26). This approach is particularly useful for the delivery of hydrophobic drugs in an aqueous solution, although hydrophilic drugs can also be coupled to the outer hydrophilic surface as well (128). For the hydrophilic segment, many amphiphilic copolymers use PEG, while for the hydrophobic segment, a variety of polyester or poly (amino acid) derivatives may be used, such as PLA or PGA (26). Polymeric micelles have several features which improve their thermodynamic stability, including increased hydrophobic segment length (129), crystallinity (130), cross-linking of the shell or core (131,132), and cohesive forces between drug and core (133,134). In addition to their ability to solubilize drugs in aqueous solution, polymeric micelles are often smaller than 50 nm in size, which allows for prolonged circulation and improved evasion of the RES.

GENEXOL-PM

Genexol-PM, also known as Cynviloq, is a polymeric micelle loaded paclitaxel formulation approved for NSCLC in South Korea. The drug was originally designed by Samyang Co, Seoul, Korea, to avoid the toxicities associated with Cremophor, the lipid based solvent traditionally used to formulate paclitaxel. Genexol-PM consists of a monomethoxy polyethylene glycol-poly (D,L-lactic acid (mPEG-PDLLA) amphiphilic diblock copolymer with a paclitaxel drug load within its hydrophobic core. In pre-clinical models, Genexol-PM displayed higher biodistribution, higher maximum tolerated dose, and higher antitumor efficacy compared to solvent based paclitaxel (14). *In vitro* studies and mouse xenograft studies have also demonstrated that Genexol-PM may be more effective at radiosensitizing compared to solvent based paclitaxel in NSCLC (135).

A phase I safety and tolerability study among 21 patients with pretreated solid tumors (eight with lung cancer), identified the MTD of 390 mg/m^2 IV on Day 1 of a 3 week cycle, with neutropenia, myalgia and neuropathy the main dose-limiting toxicities. The recommended dose was 300 mg/m^2 on Day 1 of a 3 week cycle. There were 3 PR (14%), including 2 taxane-pretreated patients (1 NSCLC) and 1 small cell lung cancer (taxane-naïve) (136). In another phase I study, 24 pretreated solid tumor patients (7 lung cancer, 11 taxane-pretreated) were treated with weekly dosing of Genexol-PM, and identified a MTD of 180 mg/m^2 IV on Days 1, 8, and 15 of a 4-week cycle. There were 5 PR (21%), including 2 with lung cancer, and 9 SD (38%) (137).

In a multicenter phase II study, 69 patients with treatment naïve advanced NSCLC were treated using a combination of Genexol-PM 230 mg/m^2 IV on Day 1 and cisplatin 60 mg/m^2 IV on Day 1 of a 3-week cycle (138). Genexol-PM was dose escalated to 300 mg/m^2 if no toxicities were observed after the first cycle. Among 69 patients, 77% had stage IV disease, and histology types included adenocarcinoma (58%), squamous (20%), large cell (3%) and other (19%). The ORR was 37.7%; 20 patients (29.0%) achieved SD. The median response duration of 26 responders was 19.8 weeks. Median TTP for all patients was 5.8 months and median OS was 21.7 months with a median follow-up of 9.6 months. Hematologic toxicity included grade III/IV neutropenia (46.4%), febrile neutropenia (3%), and grade III anemia (3%). Non-hematologic toxicity included grade III peripheral neuropathy (13%), grade III/IV myalgia (5.8%), and grade III/IV arthralgia (7.3%). There was no grade IV neuropathy. Dose reductions were required for 7 patients (10%) due to toxicity.

In another multicenter phase IIB study, the combination of Genexol-PM with cisplatin was directly compared against solvent-based paclitaxel with cisplatin (139). A total of 276 patients with advanced NSCLC were randomized to either Genexol-PM 230 mg/m^2 IV on Day 1 and cisplatin 60 mg/m^2 IV on Day 1 of a 3-week cycle (n=140) versus solvent-based paclitaxel 175 mg/m^2 IV on Day 1 and cisplatin 60 mg/m^2 IV on Day 1 of a 3-week cycle (n=136). Histology subtypes included adenocarcinoma (50.4%), squamous cell (40.2%), large cell (1.8%) and other (7.6%). ORR for the Genexol-PM arm was 44%, compared to 42% for the solvent-based paclitaxel arm. Median PFS (5.4 *vs.* 5.5 months), median OS (15.1 *vs.* 14.0 months) and 1-year survival rates (62% *vs.* 55%) were not significantly different. Incidence of grade III/IV toxicity was similar between both

arms. Grade III/IV neutropenia was higher in the Genexol-PM arm (P=0.04), but there was no significant increase in febrile neutropenia (P=0.8). As such, this study demonstrated noninferiority for Genexol-PM with cisplatin compared to standard solvent-based paclitaxel with cisplatin in NSCLC.

Genexol-PM was studied in combination with gemcitabine in a phase II study for advanced NSCLC (140). A total of 43 patients were treated with Genexol-PM at 230 mg/m^2 IV on Day 1 and gemcitabine 1,000 mg/m^2 IV on Day 1 and Day 8 of a 3-week cycle. Histology types included adenocarcinoma (65%), squamous (19%), and other (16%). Twenty-three patients (53%) were EGFR wild type, 3 patients (7%) EGFR mutant, and 17 patients (40%) were unknown. The ORR was 46.5%, with 0 CR and 20 PR. Median PFS was 4.0 months, and median OS was 14.8 months. Grade III/IV toxicity occurred in 22 patients (51.2%). Grade III/IV hematologic toxicity included neutropenia (16%) and neutropenic fever (9%). The most common grade III/IV non-hematologic toxicities were pneumonia (12%), asthenia (7%), pulmonary thromboembolism (7%), myalgia (5%), peripheral neuropathy (5%), diarrhea (2%), skin rash (2%), and dyspnea (5%).

Preliminary results from a phase II study combining Genexol-PM with carboplatin were presented at the ASCO 2014 Annual Meeting (141). A total of 80 patients with stage IIIB/IV NSCLC were treated with Genexol-PM 230 mg/m^2 IV on Day 1 and Carboplatin AUC 6 IV on Day 1 of a 3-week cycle for a maximum of 6 cycles. Clinical responses included 40.7% PR, and 48.2% SD. Hematologic toxicity was manageable, varying from grade I-III, and included 22 patients (27.5%) with grade III neutropenia.

NC-6004

NC-6004 is a 28 nm diameter, polymer-metal micellar nanoparticle composed of a hydrophilic PEG outer shell and an inner core that contains a coordinate complex of polyglutamate [P(Glu)] with cisplatin (15). In comparison to other cisplatin-containing polymeric micelles, this formulation was able to achieve a relatively much higher drug composition of 39% by weight. NC-6004 is extremely stable in distilled water with prolonged decay, and even under diluted conditions, showed a sustained release pattern >150 hours with no initial burst of drug release. NC-6004 showed prolonged plasma circulation, increased intratumoral accumulation and decreased accumulation in normal organs, when compared to standard free cisplatin in mouse models. *In vivo* antitumor activity of NC-6004 was demonstrated in mouse models of both lung and colon cancer, and interestingly, the investigators were also able to achieve complete tumor regression in 6 out of 10 mice with colon adenocarcinoma.

In a preclinical study using rodent models, NC-6004 showed decreased clearance and longer circulation time compared to standard cisplatin (142). NC-6004 achieved an AUC_{0-t} 65 times that of cisplatin (P<0.001) and a Cmax 8 times that of cisplatin (P=0.001). Meanwhile, the CLtot of NC-6004 was one-nineteenth of that of cisplatin (P<0.01). NC-6004 also showed greater tumor accumulation compared to cisplatin. Peak tumor platinum concentrations for NC-6004 occurred at 48 hours after administration, compared to 10 minutes after administration for cisplatin. Intratumoral maximum concentration (Cmax) was 2.5 times higher for NC-6004 than cisplatin (P<0.001), and intratumoral AUC was 3.6 times higher for NC-6004 than cisplatin. For gastric cancer implanted mice, NC-6004 showed antitumor activity equivalent to or greater than cisplatin. Meanwhile, NC-6004 resulted in significantly less neuropathy and nephrotoxicity compared to cisplatin. A separate preclinical study also found that NC 6004 resulted in decreased ototoxicity among guinea pigs, with decreased platinum distribution and lower platinum concentration in the organ of Corti (P<0.01), when compared to standard cisplatin (143). NC-6004 has also been found to be effective in mouse models of oxaliplatin-resistant tumors (144).

Based on these preclinical studies, an open-label, dose-escalating phase I study of NC-6004 was conducted among 17 patients with advanced solid tumors in the UK (145). Tumor types included: colon [4], lung [3], esophagus [2], melanoma [2], pancreas [2], GIST [1], renal [1], mesothelioma [1], and hepatobiliary [1]. Patients were treated with NC-6004 IV on Day 1 of a 3 week cycle, with the MTD identified as 120 mg/m^2 IV on Day 1 of a 3-week cycle and the recommended dose 90 mg/m^2 IV on Day 1 of a 3-week cycle. The maximum number of cycles received was four cycles (three patients), and mean number of cycles was 2.4. Pharmacokinetic data showed that maximum plasma concentration and AUC of ultra-filterable platinum after NC-6004 were 1/34 and 8.5 folds of those with free cisplatin. NC-6004 was well tolerated from a hematologic toxicity standpoint, with only one episode of grade III thrombocytopenia at 10 mg/m^2 and one patient with grade I thrombocytopenia at 90 mg/m^2. Regarding non-hematologic toxicity, the most common adverse events were fatigue (52.9%), nausea (47.1%), vomiting (42.1%),

and renal impairment (35.3%). There was no observed ototoxicity or neuropathy at any dose level. SD was observed in seven patients (41.2%) for longer than 4 weeks, including two patients with lung cancers. At dose levels 10-60 mg/m^2, only 2 out of 8 patients achieved SD (25%), while at doses 90-120 mg/m^2, 50% and 67% achieved SD, suggesting higher efficacy with higher doses of NC-6004. Overall, median PFS was 49 days.

A phase Ib/II dose escalation and expansion study of NC-6004 is currently enrolling patients with advanced stage IIIB/IV squamous and non-squamous NSCLC on second- or third-line therapy, as well as other patients with advanced solid tumors, to be treated with the combination of NC-6004 and gemcitabine. The primary outcomes will be maximum tolerated dose of NC-6004, and the secondary outcomes will assess overall response rate, based on CR and PR.

Conclusions

The recent introduction of immunotherapy has made a significant impact in the treatment of lung cancer, with improved outcomes including higher response rates, PFS and OS. KEYNOTE-001 treated 495 patients with advanced NSCLC using pembrolizumab, an anti-PD-1 Ab, in advanced NSCLC; the objective RR among all patients was 19.4%, with median duration of response 12.5 months, median duration of PFS 3.7 months and median duration of OS 12.0 months (7). In CheckMate 017, a total of 272 patients with advanced pre-treated squamous cell NSCLC were randomized to either anti-PD-1 therapy with nivolumab or docetaxel. Compared to docetaxel, nivolumab produced higher median OS (9.2 *vs*. 6.0 months), and higher response rates (20% *vs*. 9%). Median PFS was 3.5 months for patients treated with nivolumab (6).

While both of these studies demonstrated the utility of immunotherapy alone in NSCLC, it is unclear how to use immunotherapy in combination with chemotherapy. A phase II study randomized 204 patients with chemotherapy naïve, advanced NSCLC to treatment with carboplatin and paclitaxel plus either "concurrent" ipilimumab (anti-CTLA-4 Ab), "phased" ipilimumab, or placebo (5). "Concurrent" dosing consisted of ipilimumab given up front with the first four cycles of chemotherapy, while "phased" dosing required that the first two cycles of chemotherapy be given alone, and then ipilimumab was added for subsequent cycles. Though this study suggested a PFS benefit from "phased" dosing of ipilimumab, there is currently no standard approach to the use of chemotherapy with immunotherapy for NSCLC. More importantly, for the many patients who do not respond to immunotherapy, chemotherapy may be their only remaining treatment option. Consequently, the need to improve chemotherapy remains as vital as ever.

Targeted therapy has improved treatment of NSCLC compared to chemotherapy as well (3,4), but is also a strategy that has its limitations. EGFR mutations only occur in approximately 10-20% of North American or European populations with lung adenocarcinomas, although this number may be as high as 60% in Asian populations (146). ALK and ROS1 mutations are much less common, and occur in approximately 5% and 1% of lung adenocarcinoma, respectively (146). In addition to patients who do not have these targetable mutations, there are also patients who have mutations but develop resistance to target inhibitors. Resistance to EGFR inhibitors has been attributed to secondary EGFR mutations (T790M) in up to 60% of patients (147); other less frequent mechanisms for EGFR resistance include HER2 amplification, c-MET amplification, and PI3KCA mutations (148). In contrast, resistance to ALK inhibitors occurs due to secondary mutations in only 1/3 of cases, with other mechanisms including EGFR co-activation, KIT amplification, KRAS activation or IGF-1 receptor activation (149). For patients who develop resistance to targeted therapy, chemotherapy remains the standard for restoring responsiveness.

Chemotherapy for NSCLC has not significantly been improved since the 1990s. Systemic toxicity associated with platinum doublet chemotherapy regimens presents one of the key challenges in this arena. Nanoparticle therapies present a new arsenal of effective, but less toxic anticancer agents to fit this need. Through their unique size, nanoparticles employ the EPR effect, resulting in increased intratumoral concentrations and decreased systemic toxicity to normal tissues. Clinically these formulations demonstrate significantly better tolerability compared to standard chemotherapy formulations, including: (I) decreased cardiotoxicity for nanoparticle anthracyclines; (II) less neuropathy and renal toxicity for nanoparticle platinums; and (III) less neuropathy and myelosuppression for nanoparticle taxanes. Due to their unique size dependent properties, nanotherapies are able to carry higher amounts of cytotoxic drug, bind to multivalent ligands for improved tumor targeting, and overcome membrane pump drug resistance mechanisms, all which may contribute to higher antitumor efficacy as well. As nanotechnology improves, this should inevitably result in a growing number of new

anticancer agents, each with their own unique advantages.

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