Novel Formulations and New Mechanisms of Delivering Chemotherapy

Thomas E. Stinchcombe, MD

OVERVIEW

The identification of epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangements and the development of targeted therapy for patients with these molecular alterations has been a tremendous advance in the treatment of advanced stage or metastatic non-small cell lung cancer (NSCLC). However, the majority of patients with advanced stage NSCLC will not have one of these molecular alterations and will receive chemotherapy as their primary therapy. Chemotherapy remains a critical component of therapy for resected and locally advanced NSCLC, as well as for patients with limited-stage and extensive stage small cell lung cancer (SCLC). A significant unmet need exists to develop novel chemotherapy agents and to improve the efficacy and toxicity of currently available agents. Several novel formulations of currently available chemotherapy agents are in development for NSCLC and SCLC. Antibody conjugates are therapeutic agents that employ a tumor-specific monoclonal antibody conjugated to a cytotoxic or radionuclide agent. After the monoclonal antibody binds to the tumor antigen, these agents are internalized, and the link between the antibody and the therapeutic agent is dissolved and the cytotoxic agent is release intracellularly. This enhanced delivery of chemotherapy to malignant tissues has the potential to improve efficacy and reduce toxicity. Antibody conjugates to therapeutic agents are currently available for other malignancies and are in development for NSCLC and SCLC.

Lung cancer is the leading cause of cancer-related mortality in the United States and a leading cause of cancer-related mortality in the world.1,2 Lung cancer is divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and NSCLC is further subdivided based on histology into squamous and nonsquamous. Epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements are detected in a minority of cases of NSCLC, and the vast majority of cases of EGFR mutant and ALK rearranged NSCLC are in the nonsquamous histology.3 For patients with NSCLC that harbors an EGFR mutation or ALK rearrangement, first-line therapy with a targeted therapy is a treatment option. However, the majority of patients with NSCLC and all the patients with SCLC will receive chemotherapy as part of or the main component of their therapy. The majority of patients with lung cancer will have locally advanced or metastatic disease at the time of diagnosis, and the goals of therapy for this patient population are to extend overall survival (OS), reduce disease-related symptoms, and improve health-related quality of life. Treatment-related toxicities can adversely affect the patient’s ability to tolerate therapy or the goals of the therapy. An unmet need exists for novel chemotherapy options for patients and to improve the currently available chemotherapy agents for patients with lung cancer.

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Disclosures of potential conflicts of interest are found at the end of this article.

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NOVEL FORMULATIONS OF CHEMOTHERAPY AGENTS

New formulations of currently available chemotherapy agents have the potential to reduce toxicity and/or increase efficacy. Paclitaxel is a standard chemotherapy agent for NSCLC and uses polyoxyethylated castor oil to enhance solubility, which is responsible for the hypersensitivity reactions.4 Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a novel formulation of paclitaxel, which eliminates the polyethoxylated castor oil (Cremophor EL), thus reducing the rate of hypersensitivity reactions and eliminating the requirement for steroid premedication. Nab-paclitaxel may have greater penetration into malignant cells and the tumor microenvironment because of increased endothelial binding and transcytosis.5

A phase III trial compared carboplatin (area under the curve [AUC] of 6) and nab-paclitaxel 100 mg/m2 weekly every 3 weeks to carboplatin (AUC of 6) and standard formulation paclitaxel 200 mg/m2 every 3 weeks.6 The primary endpoint was objective response rate (ORR) by independent radiologic review (IRR). Patients in the intent-to-treat (ITT) population assigned to the nab-paclitaxel arm compared to the standard formulation arm experienced a statistically significant superior ORR (p < 0.005; Table 1). Patients in the ITT population assigned to the nab-paclitaxel compared to
the standard formulation paclitaxel experienced a similar progression-free survival (PFS) and OS. An unplanned subset was performed in 450 patients with squamous histology and 602 patients with nonsquamous histology. Patients in the squamous histology subset assigned to the nab-paclitaxel compared to standard formulation paclitaxel experienced a statistically significant improvement in ORR, but a statistically significant improvement in PFS and OS was not observed (Table 1). In the nonsquamous histology subgroup, similar ORR, PFS, and OS were observed in the nab-paclitaxel and standard formulation paclitaxel arms.

The rate of grade 3 or 4 neutropenia was lower in the nab-paclitaxel than the standard formulation paclitaxel (58% vs. 47%, p = 0.001), while the rate of thrombocytopenia and anemia was higher (18% vs. 9%, p = 0.001) and (27% and 7%, p = 0.001). In regard to nonhematologic adverse events, patients assigned to the nab-paclitaxel compared to the standard formulation paclitaxel experienced a lower rate of sensory neuropathy (3% vs. 12%, p < 0.001), arthralgia (0% vs. 2%, p = 0.008), and myalgia (< 1% and 2%, p = 0.011). Importantly the schedule and formulation of paclitaxel differed between the two treatment arms. The patient-reported outcomes were assessed using the taxane subscale of the Functional Assessment of Cancer Therapy questionnaire. Patients receiving nab-paclitaxel compared to standard formulation paclitaxel reported significantly less worsening of peripheral neuropathy (p < 0.001), neuropathic pain in the hands and feet (p < 0.001), and hearing loss (p = 0.002). Liposomal cisplatin is frequently used instead of cisplatin in chemoradiotherapy paradigms for stage IV NSCLC and extensive stage SCLC since it has lower rate of nausea, vomiting, and nephrotoxicity, but it may be a less active agent in stage IV NSCLC.

Cisplatin-based chemotherapy is the standard adjuvant chemotherapy for surgically resected NSCLC, a commonly used agent in chemoradiotherapy paradigms for stage III NSCLC and limited-stage SCLC and is a standard agent for stage IV NSCLC and extensive stage SCLC (ES-SCLC). Carboplatin is frequently used instead of cisplatin in chemoradiotherapy paradigms and for treatment of stage IV NSCLC and ES-SCLC since it has lower rate of nausea, vomiting, and nephrotoxicity, but it may be a less active agent in stage IV NSCLC.

Liposomal cisplatin is formed from cisplatin and liposomes, and preclinical studies animal studies reveal a lower rate of nephrotoxicity. A phase III trial investigated liposomal cisplatin (200 mg/m²) with paclitaxel (135 mg/m²) compared to cisplatin (75 mg/m²) and paclitaxel (135 mg/m²) every 2 weeks in patients with inoperable stage IIIA, stage IIIB, or stage IV NSCLC. The planned treatment duration was nine cycles in both treatment arms. Liposomal cisplatin was infused in 1 L of intravenous fluid over 8 hours. The study was designed with 80% power to detect a difference in nephrotoxicity, nausea and vomiting, neurotoxicity, and asthenia. Patients assigned to the liposomal cisplatin compared to the standard formulation cisplatin experienced a statistically significant lower rate of all grades neutropenia (33.3% vs. 45.2%, p = 0.017), nephrotoxicity (6.1% vs. 40.0%,

**TABLE 1. Efficacy Results of a Phase III Trial of Carboplatin and Standard Formulation and Nanoparticle Albumin-Bound Paclitaxel**

<table>
<thead>
<tr>
<th>Patient Population/Efficacy Endpoint</th>
<th>Nab-Paclitaxel</th>
<th>Standard Paclitaxel</th>
<th>Hazard Ratio or p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to treat</td>
<td>521 patients</td>
<td>531 patients</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>33%</td>
<td>25%</td>
<td>RRR = 1.313, p = 0.005</td>
</tr>
<tr>
<td>PFS (median)</td>
<td>6.3 mo</td>
<td>5.8 mo</td>
<td>HR = 0.902, p = 0.214</td>
</tr>
<tr>
<td>OS (median)</td>
<td>12.1 mo</td>
<td>11.2 mo</td>
<td>HR = 0.922, p = 0.271</td>
</tr>
<tr>
<td>Squamous</td>
<td>229 patients</td>
<td>221 patients</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>41%</td>
<td>24%</td>
<td>RRR = 1.680, p &lt; 0.001</td>
</tr>
<tr>
<td>PFS (median)</td>
<td>5.6 mo</td>
<td>5.7 mo</td>
<td>HR = 0.865, p = non-significant</td>
</tr>
<tr>
<td>OS (median)</td>
<td>10.7 mo</td>
<td>9.5 mo</td>
<td>HR = 0.890, p = 0.284</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>292 patients</td>
<td>310 patients</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>26%</td>
<td>25%</td>
<td>RRR = 1.034, p = 0.808</td>
</tr>
<tr>
<td>PFS (median)</td>
<td>6.9 mo</td>
<td>6.5 mo</td>
<td>HR = 0.933, p = non-significant</td>
</tr>
<tr>
<td>OS (median)</td>
<td>13.1 mo</td>
<td>13.0 mo</td>
<td>HR = 0.950, p = non-significant</td>
</tr>
</tbody>
</table>

Abbreviations: nab-paclitaxel, nanoparticle albumin-bound paclitaxel; ORR, objective response rate; RRR, response rate ratio; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; mo, months.

**KEY POINTS**

- The majority of patients with advanced-stage non-small cell lung cancer (NSCLC) and all patients with extensive stage small cell lung cancer (SCLC) receive chemotherapy as their primary therapy.
- Novel formulations of current chemotherapy agents have the potential to reduce toxicity and improve efficacy over previous formulations.
- Antibody-drug conjugates use an antibody against a tumor-specific antigen that is linked to a therapeutic agent to improve delivery to malignant cells and reduce exposure of normal cells.
- Antibody conjugates are currently approved for use for non-Hodgkin lymphoma, Hodgkin lymphoma, and HER2-positive breast cancer.
- Ongoing trials are evaluating the safety and efficacy of several novel formulations of chemotherapy and antibody-drug conjugates or drug conjugates in NSCLC and SCLC.
p < 0.001), nausea and vomiting (32.5% vs. 45.2%, p = 0.042), and asthenia (57% vs. 71.3%, p = 0.019). A statistically significant difference between the liposomal cisplatin and the standard formulation cisplatin in ORR, time to tumor progression, and OS was not observed. A similar trial compared liposomal cisplatin and paclitaxel to cisplatin and paclitaxel in patients with advanced disease and nonsquamous histology revealed a statistically significant improvement in ORR in the liposomal cisplatin arm (59% vs. 42%, p = 0.036). A statistically significant improvement in OS was not observed (p = 0.1551). A statistically significant lower rate of nausea and vomiting, asthenia, and nephrotoxicity was observed in the liposomal cisplatin compared to the standard formulation cisplatin arm in this trial as well (p < 0.001). The liposomal formulation of cisplatin appears to be a better tolerated formulation of cisplatin.

Cyclohextrins are cyclic oligosaccharides that are used extensively to enhance solubility, improve stability, or improve bioavailability of agents with limited solubility. Cyclohextrins have been shown to increase the cytotoxicity of camptothecin, docetaxel, paclitaxel, and SN-38, an active metabolite of irinotecan. The hypothesis is that enhanced permeability of tumor vasculature compared to normal vasculature leads to higher concentrations within malignant cells. A phase I/IIa trial of CRLX101, a cyclohextrin-containing polymer-camptothecin, in patients with solid tumors revealed myelosuppression as the dose-limiting toxicity, and the most common grade 3 or 4 adverse events were neutropenia and fatigue. The best overall response was stable disease in 28 of 44 patients (64%) treated at the maximum tolerated disease, and 16 of 22 patients with NSCLC had a best overall response of stable disease (73%). A randomized phase II trial is comparing CRLX101 to topotecan in patients with chemotherapy-sensitive or relapsed ES-SCLC (NCT01803269).

**ANTIBODY-DRUG CONJUGATE**

A limitation of chemotherapy is that normal and malignant tissues are exposed to the agent, and the normal tissue toxicity may limit the doses of chemotherapy that can be delivered or the patient’s ability to tolerate the therapy. Antibody-drug conjugate combine a tumor antigen-specific antibody covalently linked to a therapeutic agent to improve the drug delivery to the malignant cells and reduce the exposure of normal tissues. Four therapeutic strategies frequently used in development of antibody-drug conjugates are antibody-protein toxin conjugates, antibody-radiouclide conjugates, antibody small molecular drugs, and antibody-enzyme conjugates administered along with a small molecule prodrug that requires metabolism by the conjugate enzyme to release the activated agent. Early attempts to develop antibody-drug conjugates were not successful because of the immunogenicity of the antibodies, because the cytotoxic agent was either too toxic or not sufficiently potent, or because the linkers were not stable in circulation. Antibody-radiouclide conjugates that target CD-20 (I\(^{131}\)I-tositumomab and I\(^{90}\)Y-biritumomab) are currently available as treatment for non-Hodgkin lymphoma. Brentuximab vedotin (SGN-35) is a monoclonal antibody against the CD-30 that is attached to the antitubulin agent monomethyl auristatin E (MMAE) by enzyme-cleavable dipeptide linker. After brentuximab vedotin binds to the CD-30, the antibody-drug conjugate is internalized and is transported to the lysosomes, the peptide linker is selectively cleaved, and the MMAE is released into the cell. MMAE binds tubulin, which leads to cell cycle arrest. This agent is currently approved for use in patients with relapsed Hodgkin lymphoma and relapsed anaplastic large-cell lymphoma. Trastuzumab emtansine (T-DM1) is a monoclonal antibody that targets the HER2 conjugated to the DM1—a maytansine derivative that inhibits microtubule polymerization. The trastuzumab is bound to the DM1 by a thioether linker containing a cyclohexane spacer, and when T-DM1 is internalized to the cell and proteolytic digestion of the conjugate occurs, DM1’s active metabolite is released. T-DM1 has shown significant activity and a favorable toxicity profile in patients with advanced breast cancer that expresses HER2. A phase III trial compared T-DM1 to lapatinib and capcitabine in previously treated patients with metastatic HER2-positive breast cancer. Patients assigned to T-DM1 compared with lapatinib and capcitabine experienced a higher objective response rate (43.6% versus 30.8%, p < 0.001), PFS (hazard ratio (HR) of 0.65; 95% CI, 0.55 to 0.77; p < 0.001) and OS (HR of 0.68; 95% CI, 0.55 to 0.85; p < 0.001). The rate of grade 3 or 4 adverse events was lower on the T-DM1 arm (41% versus 57%). Both brentuximab vedotin and T-DM1 use a monoclonal antibody to target the malignant cell and then are internalized by the cell and undergo intracellular cleaving of the drug conjugate for cytotoxic activity. This approach localizes the cytotoxic agent to the malignant cell and reduces the normal tissue toxicity associated with cytotoxic agents.

Two previous randomized phase II trials have investigated platinum-based therapy with and without trastuzumab in patients with advanced NSCLC, and a single-arm phase II trial investigated single agent trastuzumab in the second-line setting. These trials did not suggest a benefit to the addition of trastuzumab to platinum-based therapy, but neither trial enrolled patients based on HER2 expression and only a small minority of patients enrolled had NSCLC that demonstrated HER2 overexpression by fluorescence in situ hybridization (FISH) or 3+ by immunohistochemistry (IHC). Subsequently, a phase III trial compared chemotherapy with and without trastuzumab in HER2 protein by IHC or gene amplification by FISH gastric or gastroesophageal cancer and demonstrated a statistically significant improvement in OS with the addition of trastuzumab HR of 0.74, 95% CI, 060 to 0.91; p = 0.0046). The results of this trial have raised the question about potential activity of HER2-directed therapy in NSCLC with HER2 overexpression. The rate of HER2 overexpression as defined as FISH positive or 3+ IHC is estimated to be 10% to 15%, In addition to overexpression, approximately 1% to 2% of patients with...
adenocarcinoma histology will have a mutation in exon 20 of the HER2 gene leading to constitutive activation or the receptor and downstream AKT and MEK pathways. In a retrospective case series, 16 patients with HER2 mutations received HER2-targeted therapies, and 22 individual anti-HER2 therapies were evaluable (some patients received multiple anti-HER2 therapies). For trastuzumab-based therapies (15 patients) the disease control rate (DCR) observed was 96%, and for afatinib (4 patients) the DCR was 100%. No responses were observed in the two patients treated with lapatinib and the one patient treated with masatinib. All patients received trastuzumab in combination with cytotoxic chemotherapy. The PFS observed for patients receiving HER2-directed therapies was 5.1 month, and the median OS for the 33 patients with advanced-stage disease was 22.9 months. The future development of T-DM1 in NSCLC would require a prospective trial in patients who were selected based on HER2 expression by IHC or FISH or the presence of EGFR mutation.

Lorvotuzumab mertansine is a conjugate of the cytotoxic DM1 and the CD-56 binding antibody lorvotuzumab against CD56 cells. The CD56 antigen—also called neuronal cell adhesion molecule—is expressed on a variety of hematopoietic and neuroendocrine malignancies including multiple myeloma, leukemias, lymphomas, ovarian cancer, neuroblastoma, carcinoid tumors, and SCLC. A phase I trial of lorvotuzumab mertansine that was performed in patients with CD56-positive solid tumors revealed one patient with refractory SCLC had an unconfirmed partial response and three patients with SCLC had stable disease lasting 90 days or longer. The dose-limiting toxicity observed was headache, which was not observed in later studies once steroid prophylaxis was initiated before therapy. Common grade 1 or 2 toxicities include headache, fatigue, nausea, and neuropathy (approximately 30% across multiple studies with 193 patients). The rate of grade 3 peripheral neuropathy was 2.5%, and no clinically significant myelosuppression was observed. A phase I/II trial of lorvotuzumab in combination with carboplatin and etoposide is ongoing, and the phase I portion enrolled all patients with solid tumors. The phase I portion has completed accrual, and the recommended dose of lorvotuzumab mertansine for the phase II portion is 112 mg/m² IV on days 1 and 8 in combination with carboplatin (AUC of 5) and etoposide 100 mg/m² on days 1 through 3 every 21 days. Thirteen patients with SCLC were enrolled in the phase I portion, and the ORR observed was 48.2% (6 of 13 patients). The most common grade 1 or 2 treatment-related adverse event was peripheral neuropathy, and the most common grade 3 or 4 events were related to myelosuppression (i.e., febrile neutropenia, thrombocytopenia, and neutropenia). A randomized phase II trial comparing carboplatin and etoposide alone and with lorvotuzumab mertansine is initiated (NCT01237678). This trial was stopped by the trial’s independent data monitoring committee when they thought that the investigational arm was unlikely to result in a significant improvement in PFS compared with carboplatin and etoposide. A higher rate of infection and infection-related deaths were observed in the lorvotuzumab arm. Additional data are not available at this time.

Human trophoblast cell-surface antigen (TROP-2) is expressed on multiple epithelial cancers including NSCLC. IMMU-132 is a humanized anti-TROP-2 antibody (RS7) conjugated by a pH-sensitive linker to SN-38, which is internalized into malignant cells following binding to the TROP-2 receptor allowing intracellular delivery of SN-38. Preclinical activity reveals activity in cancer xenograft models. A phase I trial is investigating IMMU-132 as single agent in previously treated patients with advanced epithelial cancer, and this trial includes an expansion cohorts for NSCLC and SCLC (NCT01631552). Folic acid is a high affinity ligand to the folate receptor, and folate receptors are highly expressed on many malignant cells. Vintafolide (EC145) is a folate conjugated to the microtubule-destabilizing agent desacetyl vinblastine—a derivative of vinblastine by disulfide linker. The folate-drug conjugate binds to the folate receptor, and endocytosis occurs, which releases the agent intracellularly with retention within the malignant cell. This agent differs from the previously discussed drug conjugates as it is bound to a folate rather than a monoclonal antibody. Folic acid–bound drugs have demonstrated greater specificity and selectivity for malignant cells in preclinical studies. A phase I trial investigated the dose-limiting toxicities, recommended dose for phase II trials, and optimal infusion time. The dose-limiting toxicity was constipation, and the common adverse events were grade 1 or 2 constipation, nausea, vomiting, and fatigue. Peripheral sensory neuropathy was observed in 28% of patients (9), and peripheral neuropathy in 6% (2). Patients were not selected based folate receptor expression, and antibody staining for the folate receptor is complicated by tumor heterogeneity, antibody nonspecificity, and reproducibility of staining. Preclinical data suggest synergy with vintafoline and docetaxel. A randomized phase II trial in the second-line setting investigating vintafoline alone, vintafoline and docetaxel, and docetaxel alone in patients with folate receptor–positive NSCLC has been developed (NCT01577654).

**CONCLUSION**

The majority of patients with NSCLC and SCLC receive chemotherapy as their primary therapy or a component of their therapy. Current chemotherapy agents are efficacious but limited by their toxicity and nonspecific delivery to both normal and malignant cells. Several agents are available or are in development that use novel formulations to improve efficacy and/or reduce the toxicity of chemotherapy. Antibody-drug conjugates are available for non-Hodgkin lymphoma, Hodgkin lymphoma, and HER2-expressing metastatic breast cancer. These agents can specifically target malignant cells and release the cytotoxic agent intracellularly to improve the delivery of the chemotherapy. Antibody-drug conjugates have the potential to improve efficacy and reduce toxicity. Multiple novel formulations and antibody-drug conjugates are currently in development for NSCLC and SCLC.
Disclosures of Potential Conflicts of Interest

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Employment or Leadership Position: None. Consultant or Advisory Role: None. Stock Ownership: None. Honoraria: Thomas E. Slinchcombe, Celgene; Genentech; Lilly. Research Funding: Thomas E. Slinchcombe, Bristol-Myers Squibb; Genentech; GlaxoSmithKline; Pfizer. Expert Testimony: None. Other Remuneration: None.

References


