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REVIEW

Novel compounds in the treatment of lung cancer: current and developing therapeutic agents

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Abstract: Lung cancer is the leading cause of cancer-related death in the United States. Though incremental advances have been made in the treatment of this devastating disease during the past decade, new therapies are urgently needed. Traditional cytotoxic agents have been combined with other modalities with improved survival for early-stage patients. Newer cytotoxic agents targeting the same or different mechanisms have been developed at different stages. Optimization of various chemotherapy regimens in different settings is one of the aims of current clinical trials. Some predictive biomarkers (eg, excision repair cross-complementing 1, ERCC1) and histotypes (eg, adenocarcinoma) are found to be associated with resistance/response to some cytotoxic drugs. Another notable advance is the addition of targeted therapy to lung cancer treatment. Targeted agents such as erlotinib and bevacizumab have demonstrated clinical benefits and gained Food and Drug Administration approval for lung cancer. More agents targeting various signaling pathways critical to lung cancer are at different stages of development. Along with the effort of new targeted drug discovery, biomarkers such as epidermal growth factor receptor and anaplastic lymphoma kinase mutations have proven useful for patient selection, and more predictive biomarkers have been actively evaluated in non-small cell lung cancer. The paradigm of lung cancer treatment has shifted towards biomarker-based personalized medicine.

Keywords: lung cancer, therapy, cytotoxic agents, targeted agents

Introduction

Lung cancer is the leading cause of cancer death in the United States, accounting for roughly one-third of all cancer deaths. It has been estimated that in 2010, there were 222,520 new cases and 157,300 deaths from lung cancer.[1]

Lung cancer is not a single disease with a single type of treatment, but rather a group of diseases that need distinct management. Lung cancer is divided into two major categories, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is the most common type of lung cancer, making up nearly 85% of all cases. It is further divided into three subcategories: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Small cell lung cancer makes up the rest. This type of lung cancer is more aggressive and almost always caused by smoking.[2]

The complexity of lung cancer makes its treatment difficult. In the past four decades since President Richard Nixon officially declared "War on Cancer", many cancers have seen their 5-year survival rates increase as a direct result of improvements in screening, diagnosis, and treatment. However, the 5-year survival rate for lung cancer has only modestly increased from 10% to 15%.[1] Much of that advance is due to better surgery and an improved ability to deliver local therapy. Some of this progress is

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due to adjuvant and neoadjuvant therapy for resectable lung cancer and, finally, some is attributable to combined-modality therapy for locally advanced disease. Until very recently, advances in therapy for metastatic disease have contributed little to the overall outcome for this disease.

The development of new classic cytotoxic agents remains an important area of clinical research in lung cancer. Optimization of chemotherapy regimens in different settings (for example, adjuvant, neoadjuvant, and maintenance) is one of the aims of current clinical trials. In addition, genetic biomarkers and histology have been actively explored to select chemotherapy for certain patient populations in order to improve efficacy and/or reduce toxicity.

Another notable advance in lung cancer is the addition of targeted drugs as a result of deeper understanding of lung cancer biology. In addition, molecular biomarkers are increasingly used to tailor treatment, and these are among the new advances that show promise in prolonging progression-free and overall survival even among those with advanced lung cancer.

Current and developing therapeutic agents for NSCLC

Cytotoxic agents

NSCLC is only moderately sensitive to chemotherapy, with single-agent response rates in the range of 15% to 30%. Most studies have shown that two agents are better than one. Three agents used in combination do not provide much additional benefit but do cause a number of additional side effects.[3] Therefore, chemotherapy regimens usually include two drugs, a platinum drug with either an older (etoposide) or newer (taxanes, gemcitabine, pemetrexed or vinorelbine) chemotherapeutic drug. Approximately 80% of all patients with lung cancer are considered for chemotherapy at some point during the course of their illness.[3]

Platinum compounds

Cisplatin has been the cornerstone of most combination regimens in advanced NSCLC. Carboplatin is another US Food and Drug Administration (FDA) approved platinum drug which causes less gastrointestinal toxicity, nephrotoxicity, and neurotoxicity but more thrombocytopenia than cisplatin.[4] American Society of Clinical Oncology guidelines recommend that first-line treatment for NSCLC should include a platinum combination.[4] In younger patients, with a good performance status or in the adjuvant setting, cisplatin is preferred, but in older patients or those with significant morbidities, carboplatin may be substituted.

Although platinum-based chemotherapy is currently the standard of care in NSCLC, data suggest that certain individual tumors may have inherent resistance to platinum compounds. Platinum disrupts the double-stranded DNA mainly through the formation of intrastrand adducts. Nucleotide excision repair (NER) is the primary DNA repair mechanism that removes platinum-DNA adducts from genomic DNA. Excision repair cross-complementing 1 (*ERCC1*) is a critical gene on the NER pathway.[5] Recent studies have found that tumors with high levels of the ERCC1 protein are less likely to respond to platinum compounds.[6] Holm et al recently reported that ERCC1 expression, as evaluated by immunohistochemistry, was associated with worse outcomes in inoperable NSCLC, particularly in men.[7] In other studies where ERCC1 mRNA expression has been measured and correlated with the outcome, results have been conflicting.[8,9] Therefore, prospective clinical studies, use of scientifically validated biomarker assays, and well-annotated clinical data will help to further define ERCC1's role in patient selection for platinum chemotherapy in NSCLC.

Development of new generation platinum compounds with improved efficacy and tolerability continues but has met challenges. The most advanced compounds, satraplatin (JM-216), and picoplatin failed to prolong overall survival in late-stage clinical trials of solid cancer.[10]

Tubulin inhibitors

Taxanes (paclitaxel and docetaxel) are microtubule stabilizing agents, and have become an integral part of several commonly used chemotherapy regimens in NSCLC. Taxanes inhibit the growth of lung cancer cell lines, exhibit synergistic interaction with other chemotherapy agents, and enhance the efficacy of radiation in vitro.[11] When used at low doses, they have important antiangiogenic properties.[12] Several Phase II and III clinical trials have established the efficacy of the taxanes, as single agents and when used in combination with a platinum compound, in the treatment of advanced NSCLC.[13–15] The use of a taxane in combination with a platinum compound has become an acceptable standard for patients with advanced or metastatic NSCLC. In addition to its efficacy in the first-line therapy of NSCLC, docetaxel is also the FDA-approved second-line agent for recurrent or relapsed NSCLC in the US. Several ongoing trials are comparing the efficacy of combining molecularly targeted agents with taxane-based regimens for the treatment of advanced NSCLC (eg, Clinicaltrials.gov identifier: NCT00976677, NCT00661193).

Recently, new formulations of taxane such as albumin-bound paclitaxel (ABI-007) and paclitaxel poliglumex have been tested in late-stage clinical trials and yielded improved toxicity profiles.[16–19] Many other novel tubulin inhibitors are at earlier stages of development and appear promising as single agents and in combination regimens. Patupilone (EPO906), ixabepilone (BMS-247550), and KOS-862 (epothilone D) are a class of epothilones that bind to the same site as taxanes, yet are structurally distinct. These epothilone agents have shown activity as second-line therapy even in docetaxel-refractory NSCLC.[20–23] ABT-751 is an agent targeting the colchicine site of tubulin. It has demonstrated activity in taxane-refractory NSCLC patients.[24] Safer and more effective tubulin inhibitors could replace paclitaxel and docetaxel as standard treatments in NSCLC in the future.

Gemcitabine

Gemcitabine, a pyrimidine nucleoside antimetabolite agent, is approved by the FDA in combination with cisplatin for the first-line treatment of patients (for whom surgery is not possible) with locally advanced (stage IIIA or stage IIIB) or metastatic (stage IV) NSCLC.

As with ERCC1 for platinum compounds, increased expression of ribonucleotide reductase subunit 1 (RRM1) may serve as a predictor for decreased response to gemcitabine. The *RRM1* gene encodes the regulatory subunit of ribonucleotide reductase which converts ribonucleotide 5′-diphosphate to deoxyribonucleotide 5′-diphosphate, which is essential for DNA synthesis. Gemcitabine, an analog of deoxycytidine (2′,2′-difluorodeoxycytidine), interferes with the function of ribonucleotide reductase and reduces the pool of deoxyribonucleotide diphosphate available for DNA synthesis. Overexpression of ribonucleotide reductase abrogates gemcitabine depletion of deoxyribonucleotide diphosphate, leading to efficient DNA synthesis and repair.[25] In a prospective Phase II study of patients with locally advanced NSCLC, increased RRM1 expression was associated with lower response rate following treatment with cisplatin and gemcitabine.[26] Other retrospective studies also demonstrated poor survival in advanced NSCLC patients with high RRM1 expression.[27–29] Trials to select chemotherapy based on RRM1 levels in advanced NSCLC are ongoing (Clinicaltrials.gov identifier: NCT00705549, NCT00499109).

Pemetrexed

Pemetrexed is approved by the FDA as a first-line treatment, in combination with cisplatin, against locally advanced and metastatic NSCLC in patients with non-squamous histology. A Phase III study showed benefits of maintenance use of pemetrexed in this histotype.[30]

Until recently, NSCLC histology was considered to have no influence on responsiveness to chemotherapy. A Phase III trial comparing first-line cisplatin–pemetrexed to cisplatin–gemcitabine in stage IIIB/IV NSCLC showed statistically similar efficacy. However, in subset analysis, patients with non squamous histology had a statistically better median survival with the cisplatin–pemetrexed combination: for adenocarcinoma (12.6 vs 10.9 months) and in large cell histology (10.4 vs 6.7 months). In contrast, patients with squamous cell histology did better with the cisplatin–gemcitabine combination (10.8 vs 9.4 months).[31] As a result, cisplatin–pemetrexed is now the preferred combination for adenocarcinoma of lung cancer.

Other cytotoxic agents

Etoposide (VP-16) has been approved by the FDA to treat SCLC. It has also been useful for NSCLC in combination with other chemotherapy drugs such as cisplatin or carboplatin. It inhibits the enzyme topoisomerase II, which unwinds DNA, and by doing so causes DNA strands to break.

Vinorelbine is an antimitotic chemotherapy drug that is given as a treatment for some types of cancer, including NSCLC.

Currently, chemotherapy alone has a limited role in curative therapy for NSCLC. For stage IIA, IIB, and IIIA NSCLC, adjuvant or neoadjuvant use of chemotherapy together with surgery have shown a survival benefit. For locally advanced NSCLC, chemotherapy may be considered as part of multimodality therapy. For stage IIIB and IV NSCLC, chemotherapy is used alone as palliative treatment.

Second-line chemotherapy can be used in selected patients with good responses to first-line chemotherapy, good performance status, and a long disease-free period between initial chemotherapy and relapse. Docetaxel and pemetrexed have been approved by FDA in this clinical setting, but other drugs (eg, gemcitabine, vinorelbine), if not used in the first-line regimen, may result in similar clinical benefit.[4]

The concept of maintenance therapy has been introduced in recent years for NSCLC treatment. Multiple clinical trials have been conducted with maintenance therapy following four to six cycles of first-line chemotherapy. These trials have shown improvement in progression-free survival or even overall survival using agents (pemetrexed, docetaxel, and erlotinib) approved as second-line therapy.[32,33]

Targeted agents

With the increased understanding of molecular abnormalities in lung cancer, recent research efforts have focused heavily on identifying molecular targets and using this knowledge to develop molecular-targeted therapies. An important advancement in lung cancer treatment has been the development of such targeted therapies. Targeted treatments attack cancer in more specific ways, usually by interrupting the signaling pathways critical to cancer cell proliferation and survival.

Targeting epidermal growth factor receptor

Dysregulation of epidermal growth factor receptor (EGFR) is one common abnormality in NSCLC. Stimulation of the EGFR pathway leads to a series of intracellular events culminating in increased mitotic and growth potential, increased ability to metastasize, and increased angiogenesis in the cancer. Cancers with EGFR overexpression have been shown to be associated with increased resistance to therapy, increased metastatic potential, and poorer prognosis.[34]

Gefitinibis the first EGFR tyrosine kinase inhibitor (TKI) entering clinical trials for NSCLC. It binds reversibly to the adenosine triphosphate (ATP) binding site of the EGF receptor, blocking signal transduction to downstream molecules.[34]

In two large Phase II trials, IDEAL1 and IDEAL2 (Iressa Dose Evaluation in Advanced Lung Cancer), single-agent gefitinib achieved objective tumor responses of 18.4% and 11.8%, and disease control rates (complete and partial responses plus stable disease) of 54.4% and 42.2%, respectively, in recurrent advanced NSCLC.[35] Based on these promising results, gefitinib was granted accelerated FDA approval as a third-line therapy in May 2003.[36] However, results from a subsequent large Phase III randomized clinical trial (Iressa Survival Evaluation in Lung Cancer, ISEL) showed that gefitinib did not provide a survival benefit over placebo for the majority of participants.[37] As a result, in June 2005, the FDA limited the use of gefitinib to those patients who were benefiting from treatment, and for use in clinical trials.

In August 2009, the results of a Phase III trial called IPASS (Iressa Pan Asia Study) comparing gefitinib with carboplatin–paclitaxel in the first-line setting in Asian patients who had adenocarcinoma and who had never smoked or who were former light smokers (none in the prior 15 years), were reported.[38] Gefitinib demonstrated better progression-free survival compared with the combination chemotherapy of carboplatin and paclitaxel. Patients receiving gefitinib had a higher response rate (43% vs 32%), with similar median survival (18.6 vs 17.3 months). Patients who were positive for the *EGFR* gene mutation (n = 261) experienced significantly longer progression-free survival when enrolled in the gefitinib group compared with those who received carboplatin–paclitaxel. Conversely, patients who were negative for the mutation (n = 176) had significantly longer progression-free survival in the carboplatin-paclitaxel group. This marked the first time a single targeted therapy has shown significantly longer progression-free survival over chemotherapy. Currently, gefitinib remains an approved treatment in Europe and in 36 other countries for NSCLC whose tumors have tested positive for the *EGFR* mutation.

Erlotinib is another EGFR inhibitor with a similar mechanism of action to gefitinib.[39] In a randomized, placebo-controlled, double-blind trial (BR.21; N = 731) to determine whether erlotinib prolongs survival in NSCLC after failure of first-line or second-line chemotherapy, erlotinib demonstrated improved response rates (8% vs <1%), and overall survival (6.7 vs 4.6 months) compared with the placebo group.[40] This led to the FDA approval of erlotinib in the second-line setting in 2004.

The efficacy and safety of erlotinib as maintenance treatment of NSCLC were later demonstrated in a randomized, double-blind, placebo-controlled trial called SATURN (Sequential Tarceva in Unresectable NSCLC) conducted in 26 countries, in 889 patients with locally advanced or metastatic NSCLC whose disease did not progress during first-line platinum-based chemotherapy.[41] Patients were randomized 1:1 to receive erlotinib 150 mg or placebo orally once daily until disease progression or unacceptable toxicity. The primary objective of the study was to determine if the administration of erlotinib after standard platinum-based chemotherapy in the treatment of NSCLC resulted in improved progression-free survival when compared with placebo, in all patients or in patients with EGFR immunohistochemistry-positive tumors. The results show that compared with placebo, erlotinib maintenance therapy significantly improves progression-free survival (12.3 vs 11.1 weeks) and overall survival (12.0 vs 11.0 months) in patients with advanced NSCLC. Based on the SATURN results, the FDA in 2010 expanded erlotinib's approval to maintenance use for locally advanced or metastatic NSCLC that has not progressed after four cycles of platinum-based first-line chemotherapy.

Erlotinib is currently being tested in a wide variety of clinical trials for NSCLC, including as a first-line treatment; early stage treatment; in combination with chemotherapies; and after surgical removal of lung cancer.

The finding that the *EGFR* activating mutation is closely associated with sensitivity to EGFR tyrosine kinase inhibitors

revolutionized the care of patients with lung cancer. Earlier studies with either erlotinib orgefitinib showed better response rates and survival with females, individuals of Asian descent, and nonsmokers, particularly those with adenocarcinoma histology, and among them, especially those with bronchioalveolar cancer.[36,41] Research subsequently showed that *EGFR* activating mutations (mainly exon 19 deletions or L858R mutation) confer tumor sensitivity to EGFR tyrosine kinase inhibitors and these mutations are more frequent in the subpopulations of NSCLC patients mentioned above.[42,43] These mutations occur in 10% of lung adenocarcinoma specimens in the United States and in 30% in Asian samples. Since these observations were first made, it has become clear that the best predictor of a meaningful clinical response to EGFR TKI is the presence of *EGFR* activating mutations in the tumor, so that, pretreatment testing for *EGFR* mutation via direct sequencing or mutation-specific detection, is now endorsed by many leading institutions. It has become common practice that NSCLC patients positive for *EGFR* activating mutations are treated with EGFR TKI as frontline therapy, which is supported by multiple Phase II and III clinical trials of both erlotinib and gefitinib including the IPASS trial as described above.[35,44–46]

Neratinib (HKI-272) is one of the second generation-EGFR/HER2 tyrosine kinase inhibitors with a quinazoline core structure that can irreversibly bind to the ATP pocket of EGFR kinase. It was designed, potentially, to overcome secondary resistance to erlotinib or gefitinib. The secondary EGFR kinase mutation T790M accounts for roughly 50% of cases of acquired resistance. Laboratory studies have indicated that HKI-272 can inhibit the growth of lung cancer cells bearing *EGFR* T790M mutation, suggesting a potential benefit for patients with this mechanism of acquired resistance to erlotinib.[47] However, the clinical efficacy of these irreversible inhibitors has been limited by toxicities, such as diarrhea and rash, associated with wild-type EGFR inhibition.[48] Interestingly, WZ4002, an early development compound with a pyrimidine core structure, can strongly inhibit T790M EGFR without affecting wild-type EGFR in cultured cells, in contrast to the quinazoline-based inhibitors.[49] Its clinical utility has yet to be confirmed.

Another strategy to overcome *EGFR* T790M mutation is to target heat shock protein 90 (HSP90), a molecular chaperone for many oncoproteins critical to cancer.[50] It has been demonstrated that HSP90 inhibitors can downregulate multiple oncoproteins including mutated *EGFR* in lung cancer cell lines bearing an T790M mutation, and prolong the survival of mice carrying orthotopic lung tumors established from *EGFR* T790M-mutant cell lines.[50,51] Currently, a few HSP90 inhibitors are being evaluated broadly in clinical trials. These agents include the natural product 17-AAG (17-allylamino-17-demethoxygeldanamycin) and its derivative IPI-504, and the small-molecule inhibitor Debio-0932 (formerly CUDC-305).[51–53] By overcoming gatekeeper residue mutations, such a strategy, if successful, may be of value for the treatment of a broad range of mutant receptor-driven cancers.

Among the means of acquired resistance to EGFR inhibitors, the T790M mutation mechanism only accounts for 50% of all cases. Another mechanism is the activation of alternative receptor tyrosine kinase pathways (eg, MET, IGFR, PDGFR), thereby bypassing EGFR signaling.[54] Such compensatory mechanisms also often play an important role in primary resistance to EGFR TKI, which after all occurs in most NSCLC cases. One strategy to overcome primary and/or secondary resistance is the use of multitargeted agents that can interrupt multiple signaling nodes/pathways simultaneously. CUDC-101, a small-molecule inhibitor of the histone deacetylase, EGFR and HER2, is designed to overcome EGFR TKI resistance by blocking key regulators of several compensatory signaling pathways, in addition to its direct targets, EGFR/HER2 signaling pathways.[54,55] Currently, the compound is being tested in Phase IB clinical trials for solid tumors including NSCLC (Clinicaltrials.gov identifier: NCT01171924).

Besides EGFR TKI, monoclonal antibody against EGFR extracellular domain is another approach to targeting EGFR pathway. Cetuximab, a chimeric human-murine monoclonal antibody against EGFR, has been approved to treat colorectal and some head and neck cancers. Data released in June 2008 show survival advantages in NSCLC patients in the first-line setting.[56] In this study of 1125 patients with advanced NSCLC expressing EGFR by immunohistochemistry (First-Line Treatment for Patients with Epidermal growth factor inhibitor EGFR-EXpressing Advanced NSCLC, FLEX), those given the combination treatment (cisplatin-vinorelbine plus cetuximab) lived an average of 11.3 months vs 10.1 months for those who received only chemotherapy (cisplatin–vinorelbine). Further studies on molecular markers to predict response are ongoing, and will be required to determine optimal strategies for the use of these agents in a manner that generates more meaningful clinical benefits. It has recently been shown that colon cancer patients who have a mutation of *KRAS*, do not derive a benefit from cetuximab treatment. This finding has changed the practice of cetuximab use in colon cancer.[57] However, it does not

seem that the same applies to NSCLC yet.[58] Rather, further studies are needed to delineate which biomarkers have values in making treatment decision for NSCLC.

Synergy between cetuximab and radiation therapy has been observed in head and neck cancer.[59] This combination is currently being investigated in NSCLC and may or may not confirm synergy in this indication.

Targeting angiogenesis

Angiogenesis is the process by which new blood vessels grow from pre-existing vessels. This critical step enables tumor expansion, local invasion, and dissemination.[60] As a result, targeting angiogenesis has become an attractive approach in cancer treatment. An extensive array of antiangiogenic compounds is currently in preclinical development, with many now entering the clinic and/or achieving FDA approval. Presently, the monoclonal antibody bevacizumab is an approved treatment for NSCLC. The kinase inhibitors vandetanib, sunitinib, and sorafenib are currently in late-stage clinical trials.

Bevacizumab was approved in October 2006 for use with chemotherapy (carboplatin and paclitaxel) in patients with NSCLC that is not surgically removable and is locally advanced, recurrent, or metastatic. Bevacizumab, however, is not appropriate for use in patients with squamous cell carcinoma.

A Phase III ECOG (Eastern Cooperative Oncology Group) study in 878 patients with recurrent or advanced NSCLC has shown that addition of bevacizumab to standard first-line carboplatin–paclitaxel resulted in significant prolongation of survival.[61] The median overall survival was improved (12.3 vs 10.3 months), as was the response rate (35% vs 15%) compared with chemotherapy alone. Despite increased hemorrhagic complications and treatment-related deaths, bevacizumab has now been approved for use in this setting in combination with chemotherapy.

Bevacizumab in combination with cisplatin–gemcitabine has also been studied in a Phase III trial (Avastin in Lung, AVAiL) as first-line therapy for non-squamous NSCLC, and yielded modest improvement in progression-free survival (6.7 vs 6.1 months), but not overall survival.[62]

Numerous studies have focused on identifying subpopulations that may benefit from the addition of bevacizumab to chemotherapy. As in other cancer indications, hypertension is emerging as a predictor of clinical benefit from bevacizumab in NSCLC (ECOG 4599).[63]

Sunitinib is a small-molecule inhibitor of VEGF receptor (VEGFR) 1, VEGFR-2, fetal liver tyrosine kinase receptor 3 (FLT3), stem cell factor receptor (KIT), and platelet-derived growth factor receptor-alpha/beta (PDGFRα/β).[64] This compound has been approved to treat metastatic renal cell carcinoma (RCC). A Phase II study of sunitinib in refractory NSCLC demonstrated single-agent activity in previously treated patients with recurrent and advanced NSCLC, with a level of activity similar to currently approved agents.[65] However, clinical trials with sunitinib have raised concerns over its toxicity.[66] Furthermore, a trial of sunitinib in combination with erlotinib vs erlotinib alone (SUN1087) demonstrated a statistically significant improvement in progression-free but not in overall survival, in patients with previously treated advanced NSCLC.[67] Nonetheless, sunitinib as maintenance therapy in previously treated advanced NSCLC is being investigated (Clinicaltrials.gov identifier:NCT00693992).

Sorafenib is another small-molecule inhibitor of the multiple kinases involved in angiogenesis and is currently marketed worldwide for the treatment of hepatocellular carcinoma, and advanced RCC.[68] Unfortunately, in a Phase III trial named NExUS (NSCLC research Experience Utilizing Sorafenib) evaluating sorafenib vs placebo in combination with two chemotherapeutic agents, gemcitabine and cisplatin, in patients with advanced NSCLC, sorafenib did not meet the primary endpoint of improving overall survival in the first-line setting, though a positive secondary endpoint of progression-free survival was observed.[69] Currently, sorafenib is being evaluated in a variety of treatment settings for patients with NSCLC, including a Phase III monotherapy study in the third- and fourth-line setting and Phase II studies in combination with other therapies as second-line treatment.[70]

Vandetanib is a small-molecule inhibitor of the VEGFR, EGFR, and rearranged during transfection (RET) tyrosine kinases.[71] It has been tested as second-line treatment combined with docetaxel in a Phase III trial (ZODIAC),[72] as second-line treatment combined with pemetrexed in a Phase II randomized trial (ZEAL),[73] as second- or third-line treatment compared with erlotinib in a Phase III trial (ZEST),[74] and second-line treatment compared with placebo in previously treated patients in a Phase III trial (ZEPHYR).[75] The results indicate that vandetanib has some activity, but lacks overall survival improvement. It was initially submitted to FDA in June 2009 for approval in combination with chemotherapy in patients with advanced NSCLC. However, the application was withdrawn in October of the same year for lack of benefit when administered along with chemotherapy.

Targeting EML4-ALK

The EML4-ALK mutation, a fusion of the anaplastic lymphoma kinase (ALK) with echinoderm microtubule-associated protein-like 4 (EML4), has been identified in roughly 6% of NSCLC cases.[76,77] Several clinical features, including no or light history of smoking, male gender, younger age (median age approximately 50), lack of *EGFR* or *KRAS* mutation and an adenocarcinoma history, are associated with the *EML4-ALK* mutation.[78–80] Therefore, a trial can be enriched for a patient population with *EML4-ALK* mutation by these clinical features.[78] PF-02341066 (crizotinib), a small-molecule inhibitor of c-MET and ALK, is the most advanced ALK inhibitor in development.[81–83] In a Phase I/II trial, impressive results have been reported in patients with underlying *EML4-ALK* mutation. EML4-ALK fusion was found in 19 out of 141 patients. Among them, 10/19 (53%) demonstrated drug response and disease stabilization at 8 weeks, lasting up to 40 weeks. The side effects associated with PF-02341066 treatment seemed tolerable.[83] The trial strongly suggests the importance of incorporating prospective molecular enrichment strategies for patient selection which may be generally useful in future clinical trials for targeted therapies.[84] Based on this promising observation, several other clinical studies including Phase III trials on patients restricted to those with EML4-ALK fusion mutation, have been initiated (Clinicaltrials.gov identifier: NCT00932893). Results from these trials are awaited.

Targeting IGF-1 and IGF-1R

The insulin-like growth factor 1 (IGF-1) receptor (IGF-1R) is anovel target for cancer therapy since high level expression of IGF-1R occurs in up to 70% of NSCLC patients.[85,86] IGF-1R signaling involves the activation of intracellular pathways including the RAS/RAF/MAP kinase and the PI3K (phosphatidylinositol-3-kinase) pathways, all of which are critical to cancer proliferation and survival.[87]

CP-751,871 (figitumumab), a monoclonal antibody against IGF-1R, has been assessed in a randomized Phase II study in patients with advanced NSCLC without prior treatment.[88] In this study, 156 patients were enrolled to receive carboplatin and paclitaxel with or without two doses of CP-751,871 (10 mg/kg or 20 mg/kg). Objective response was observed in 54% of patients treated with a combination of antibody and chemotherapy, versus 42% of patients treated with chemotherapy alone. In addition, the response rate was highest (78%) in patients with a squamous histology in the high dose CP-751,871 arm, suggesting dysregulation of IGF-1R pathway may be common in this histotype.[89] Additionally, there was a trend towards improved progression-free survival in the high dose group.[88] A randomized, open-label, Phase III trial assessing IGF-1R antibody and chemotherapy in combination was planned but withdrawn prior to enrollment (Clinicaltrials.gov identifier: NCT00907504).

Besides monoclonal antibodies, several small-molecule inhibitors of the IGF-1R tyrosine kinase are also tested at various development stages in solid tumors including NSCLC (AEW541, OSI-906, BMS-536924, etc).[90]

Targeting c-MET

MET is a proto-oncogene encoding a heterodimeric transmembrane receptor. The MET kinase receptor and its ligand are responsible for key intracellular signaling cascades associated with cell growth, proliferation, invasion, and angiogenesis.[91] Overexpression of c-MET is found in 60% to 80% of NSCLC patients, and 20% of them carry c-MET mutations.[92] Amplification of c-MET also occurs in acquired EGFR TKI-resistant NSCLC patients without *EGFR* mutations (eg, T790M), suggesting that c-MET may be a relevant target for some NSCLC patients with resistance to gefitinib or erlotinib.[93] Simultaneous targeting of c-MET and EGFR may serve as a treatment strategy for NSCLC since coactivation of both receptor pathways is frequently observed.[94] Several c-MET antagonists are currently under clinical investigation. The most advanced is PF-02341066, a multi-kinase inhibitor that has demonstrated an overall response rate of 53% and disease control of 79%, at 8 weeks in NSCLC.[95] At present, this compound is in Phase II/III clinical development in NSCLC patients at a dose of 250 mg twice daily either in monotherapy or in combination with EGFR inhibitors (Clinicaltrials.gov identifier: NCT00932893, NCT00932451, NCT00965731).

Other small-molecule multi-kinase inhibitors, such as XL-184, ARQ197, and MK-2461 have also entered clinical trials in NSCLC.[92]

Finally, SCH-900105 (AV-229), a humanized monoclonal antibody, and AMG102, a fully human monoclonal antibody against free HGF (hepatocyte growth factor, the ligand for c-MET), are being tested in Phase I and II clinical trials in lung cancer in combination with EGFR TKI (Clinicaltrials.gov identifier: NCT01039948, NCT01233687).[92]

Targeting the PI3K/AKT/mTOR pathway

The PI3K signaling pathway is crucial in cell proliferation, survival, metabolism, and apoptosis inhibition.[96] Abnormalities in PI3K/AKT/mTOR pathway are implicated in many cancers, including NSCLC.[97] This pathway is typically activated at an early stage in the development of

lung cancer, suggesting that it may be a relevant target for NSCLC therapy.[98]

Intriguingly, a number of signaling nodes of the PI3K pathway can be targeted individually for cancer therapy. Inhibitors of these molecular targets have shown activity in NSCLC cell lines in vitro and in vivo, and some compounds have entered early clinical trials.[99]

The serine-threonine kinase mTOR downstream of PI3K-AKT plays a critical role in signaling caused by activation of upstream receptor tyrosine kinases.[99] Rapamycin derivatives of the mTOR complex 1 (mTOR1) inhibitors, temsirolimus (CCI-779) and everolimus (RAD001), have been approved for the treatment of metastatic RCC and are currently being evaluated in NSCLC. Antitumor activity has been observed with several of these inhibitors in Phase I/II studies in NSCLC.[100–105] Of note, a Phase I study with everolimus has shown inhibition of the proangiogenic growth factors in response to radiation-induced stress.[100] However, a subsequent Phase II study with everolimus therapy alone has been disappointing.[101] Everolimus is also being evaluated in NSCLC in combination with erlotinib or gefitinib, and docetaxel in relapsed NSCLC.[103,104]

Another mTOR inhibitor, temsirolimus, has been assessed in SCLC as maintenance therapy, but also concluded with disappointing results.[102] Two Phase II studies of temsirolimus as monotherapy or in combination with pemetrexed, are being conducted in advanced or refractory NSCLC (Clinicaltrials.gov identifier: NCT00079235, NCT00921310). A novel mTOR inhibitor, ridaforolimus, formerly known as AP23573 and MK-8669, is currently being investigated in a Phase II study in NSCLC patients with *KRAS* mutations (Clinicaltrials.gov identifier: NCT00818675) after partial response was observed in a Phase I trial in NSCLC.[105]

Kinase inhibitors that target both mTOR complex 1 and 2 (mTORC2) are believed to be more effective than the current rapamycin analogs. OSI-027 and AZD8055, two ATP-competitive inhibitors of the mTORC1 and mTORC2, are currently in early clinical trials for solid tumors and lymphoma (Clinicaltrials.gov identifier: NCT00698243, NCT00731263).

Numerous compounds targeting PI3K have been introduced into clinical trials. BEZ235, animidazoquinoline derivative and dual PI3K/mTOR inhibitor, was the first to enter the clinic in 2006. Dual PI3K/mTOR inhibitors XL765, GDC-0941, BGT226, and single PI3K inhibitors BKM120, XL147, GSK1059615, are also under clinical development.[99] Simultaneous inhibition of both PI3K and mTOR might potentially increase inhibition of signaling throughout the pathway's cascade of signaling events.

Targeting KRAS

EGFR and *KRAS* are the two most commonly mutated oncogenes in lung cancer. *KRAS* links *EGFR* signaling to intracellular molecules involved in cell proliferation and survival. Mutations in *KRAS* are found in approximately 15% of advanced NSCLC patients. Activating mutations in *KRAS* can bypass *EGFR* signaling and mediate the resistance to EGFR inhibitors.[106–108]

There are no approved KRAS inhibitors on the market today for the treatment of lung carcinomas. However, the development of therapeutic agents targeting KRAS inhibition continues. MT477, a novel quinoline with both in vivo and in vitro inhibition activities against cell lines with mutated KRAS, might have potential for future development as an agent targeting *KRAS* mutant tumors.[109] Clinical trials of a farnesyl transferase inhibitor which alters RAS membrane localization have not demonstrated efficacy in *KRAS* mutant tumors.[110] Molecular targets downstream of KRAS, such as MEK and RAF, have also been actively evaluated, so far with little promise.[111,112]

Targeting polo-like kinases

Polo-like kinases (PLKs) are highly conserved serine/threonine kinases which control cell division. PLK mRNA is highly expressed in most cancers, but not in surrounding healthy noncancer cell types, making it an attractive target in cancer treatment.[113,114] Several PLK inhibitors have been tested in clinical trials for treatment of cancer. Among them, BI2536 and BI6727 are the most advanced.[115] In a Phase II study in NSCLC patients, BI2536 was delivered on day 1 (200 mg) or on days 1–3 (3×50 mg/$^3 \times 60$ mg) on a 21-day treatment program. Clinical benefit was observed in 54% of patients. Adverse events, including nausea and fatigue, were mild.[116] BI6727, a follow-up compound with improved pharmacological profiles over BI2536, is being tested in combination with pemetrexed in advanced NSCLC (Clinicaltrials.gov identifier: NCT00824408).[117] Several other PLK inhibitors, including HMN-214, ON019190.Na, and GSK461364 have also entered clinical trials for lung cancer.[114,118,119]

Proteasome inhibitors

Proteasome inhibitors have effective antitumor activity in cell culture, where they induce apoptosis by disrupting the regulated degradation of pro-growth cell cycle proteins.[120] Bortezomib is a dipeptidyl boronic acid that serves as a spe-

cific and selective reversible inhibitor of the 26S proteosome and has been approved for the treatment of multiple myeloma.[120] A Phase II study of 114 NSCLC patients treated with bortezomib plus gemcitabine/carboplatin showed 1-year and 3-year survival rates of 47% and 19%, respectively.[121] A subsequent Phase II trial with monotherapy of bortezomib in chemotherapy-naïve patients with advanced stage NSCLC has seen modest results, suggesting that bortezomib is most likely to gain clinical value in combination with other therapeutic agents.[122] Clinical trials testing bortezomib in combination with cytotoxic or targeted agents in NSCLC are ongoing.

Alternative approaches

Several types of vaccines for boosting the body's immune response against lung cancer cells are being tested in clinical trials. These vaccines are designed to help treat, not prevent, lung cancer, in contrast to traditional vaccines such as those used to prevent infections like measles or mumps. Due to limited side-effects, these types of treatments may be useful in people who cannot tolerate other treatments. Vaccines can be made from lung cancer cells or cell components, such as parts of proteins commonly found in cancer cells. For example, L-BLP25 is a vaccine made up of Mucin 1 protein commonly expressed in NSCLC. A small study in 171 patients with advanced NSCLC suggested that it may improve survival time.[123] Three larger Phase III trials are being conducted worldwide to confirm this possibility. Other vaccines such as those directed against N-glycolyl-GM3 ganglioside, Toll-like receptor-9, EGFR, granulocyte macrophage colony stimulating factor, and melanoma-associated antigen (MAGE)-A3 are also being evaluated in clinical trials in NSCLC.[124]

Gene therapy has become an attractive approach following the discovery of gene dysregulation in lung cancer. The gene therapy approach is still not validated and only limited clinical activity has been observed in clinical trials. Gene targeting strategies include introducing suicide genes, replacing defective tumor-suppressor genes, or inactivating oncogenes. The most extensively tested gene therapy is the replacement of the p53 gene which is mutated in 40% to 70% of NSCLC samples and which is associated with resistance to chemotherapy and radiotherapy.[125] Phase I studies of p53 replacement with various viral vectors injected directly or delivered by bronchoalveolar lavage have suggested clinical response with evidence of targeted gene expression in lung tumor lesions.[126,127] However, a large Phase II study indicated that recombinant adenovirus p53 (Ad. P53) provides little benefit over chemotherapy.[128] Until more efficient vectors are developed, the potential for gene therapy in NSCLC is very limited.

Photodynamic therapy is currently in clinical trials for patients with limited SCLC whose cancer is causing an endobronchial obstruction.[129,130] The photosensitizing agent, typically comprising a porphyrin, a naturally occurring substance in the body, is first injected into the patient a few hours before surgery. The agent then selectively accumulates in rapidly growing cells such as cancer cells. During surgery, a certain wavelength of light which activates the photosensitizing agent is applied causing the production of a toxin that accumulates in the cancer cells and ultimately destroys them.

Current and developing therapeutic agents for SCLC

Chemotherapy is the cornerstone for SCLC treatment. In limited stage disease, chemotherapy and radiotherapy are often used together. Extensive stage disease is treated primarily with combination chemotherapy.[131]

Cytotoxic agents

Many chemotherapy agents are active against SCLC. Combination chemotherapy of two to three agents has been proven to be more effective in SCLC than single drug therapy. Reported response rates range from 80% to 100% for limited disease and 60% to 89% for extensive disease.[131] The most commonly used two-drug combination is a platinum compound plus etoposide, whereby four to six cycles of treatment are typically administered.[131] Ongoing clinical trials focus on examining the effectiveness of different chemotherapy combinations using established and newer chemotherapy agents. High doses of chemotherapy followed by a bone marrow transplant have also been explored.[132] Two studies have indicated that high-dose chemotherapy plus autologous stem cell transplant improve progression-free survival and overall survival in patients with limited SCLC.[133,134] Listed below are a few newer cytotoxic agents that have been added to the arsenal of treatment choices in recent years.

Topotecan is a semisynthetic derivative of camptothecin and is an antitumor drug with topoisomerase I-inhibitory activity.[135] The pill form of topotecan was approved in October 2007, for the treatment of relapsed SCLC patients with a prior complete or partial response who are at least 45 days from the end of first-line chemotherapy. Injectable topotecan has been an approved treatment for SCLC since 1998.

Amrubicin (SM-5887) is the hydrochloride salt of a third-generation synthetic 9-amino-anthracycline with antineoplastic activity. Amrubicin intercalates into DNA and inhibits the activity of topoisomerase II, resulting in the inhibition of DNA replication, and RNA and protein synthesis, followed by cell growth inhibition and cell death. This agent has demonstrated a higher level of antitumor activity than conventional anthracycline drugs without exhibiting any indication of the cumulative cardiac toxicity common to this class of compounds.[136] Amrubicin was granted fast-track designation by FDA in September 2008 for SCLC treatment after first-line chemotherapy.

Targeted agents

Targeted drugs have been explored in combination with chemotherapy, but have yielded inconclusive results. Currently, a few randomized clinical trials are ongoing to further assess targeted agents in SCLC. To date, it is generally accepted that the administration of targeted agents as induction treatment of SCLC does not improve the outcomes reached with chemotherapy alone. Targeted agents tested in this setting include the KIT inhibitor STI-571, the Bcl-2 antisense agent G3139, and the antiangiogenesis antibody bevacizumab.[137–139] Targeted agents have also been tested as maintenance/consolidation therapy, for instance, the matrix metalloproteinase inhibitors BB2516 (marimastat) and BAY 12-9566 (tanomastat), the immune stimulator BEC2 (mitumomab), the VEGFR/EGFR/HER2 tyrosine kinase inhibitor ZD6474 (vandetanib), immunomodulatory and the antiangiogenic compound thalidomide. However, no positive result has been reported in this setting.[140–145]

Conclusion

Over the past few years, advances have been made in the treatment of lung cancer mainly due to the addition of targeted agents and the use of multimodality therapies. In addition, predictive biomarkers such as *EGFR* and *ALK* mutations help greatly to tailor targeted agents to the appropriate patient population. Even for traditional chemotherapeutic agents, biomarkers such as ERCC1 can help in patient selection in order to reduce toxicity and improve efficacy. Many clinical trials are ongoing to define the roles of targeted therapies along with relevant biomarkers, and to optimize regimens of multimodality therapies in different settings in lung cancer. It will be exciting to see the results from these trials during the next few years and whether truly significant improvements of overall and progression-free survival can be achieved.

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