symposium article

Newer opportunities in systemic therapy of lung cancer

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introduction

Lung cancer continues to be the leading cause of cancer mortality despite steady improvements in treatment modalities over the last few years. Five-year survival remains unacceptably low at about 15%. Most patients who present with advanced disease can only be treated with palliative intent since the disease is not curable at this stage. Patients with locally advanced or metastatic disease are treated with systemic chemotherapy if they have a good performance status. First-line therapy consists of a platinum-based doublet, with or without bevacizumab, depending on histology and bleeding risk. In recent years a wealth of knowledge has become available on the molecular alterations associated with the development of lung cancer. Based on our understanding of the biology of lung cancer, targeted therapies have been developed and incorporated into currently existing treatment regimens. The most important examples that illustrate this fact are the anti-angiogenic agents such as bevacizumab and the epidermal growth factor receptor (EGFR) antagonists such as erlotinib. However despite these advances it is becoming increasingly clear that lung cancer is a complex disease, or indeed a heterogeneous group of diseases at the molecular level. Therefore, to develop truly effective systemic therapies, it is absolutely essential to know the molecular pathogenesis of the disease. The aim of this review is to illustrate key molecular pathways responsible for development of non-small cell lung cancer (NSCLC), and the way that drugs have been developed against potential targets involved in these pathways.

epidermal growth factor receptor

A key contributor to malignant transformation leading to lung cancer is EGFR. The EGFR is a member of a family composed of four receptors; EGFR (also known as ERBB1 or HER1), HER-2 (or ERBB2), HER3 and HER4 [1]. Aberrant functioning of these transmembrane receptor tyrosine kinases (RTKs) leads to activation of intracellular signaling cascades leading to cell proliferation and survival. EGFR is overexpressed in about 70% of NSCLCs and HER2 is overexpressed in about 30% of NSCLCs [2]. In addition, mutations have been described in the tyrosine kinase domain of EGFR in about 10% of NSCLCs in Caucasians and 25–50% in Asians [3]. Mutations and amplification of HER2 are very rare in NSCLC. Single-agent tyrosine kinase inhibitor (TKI) therapy against EGFR (gefitinib and erlotinib) has yielded response rates of 10–18% [4]. The only positive randomized phase III trial of TKIs administered in

patients who had received prior platinum-based therapy was the BR21 trial in which a median survival advantage of 2 months was seen with erlotinib therapy, compared with placebo [5]. The corresponding trial with gefitinib (ISEL study) did not show a significant survival advantage [6]. Among the various markers of response to TKI therapy are, mainly, the presence of EGFR mutations and EGFR amplification. The presence of EGFR activating mutations dramatically increases the response rate to TKI therapy and this may be as high as 75–90% with median survival of up to 30 months [3, 4]. In contrast, the presence of KRAS mutations, the point mutation T790M in exon 20 of EGFR, as well as amplification of MET, render patients resistant to EGFR TKI therapy [7, 8, 9]. Second-generation TKIs are being developed to circumvent this problem. They are mainly represented by irreversible EGFR inhibitors and inhibitors of additional kinases [10, 11].

vascular endothelial growth factor

One of the key requirements for sustained growth of tumors is the ability to stimulate angiogenesis. Vascular endothelial growth factor (VEGF) plays a central role in angiogenesis. Studies have shown that increased levels of VEGF in tumors and in circulation are associated with poor survival in lung cancer [12, 13]. The biologic actions of VEGF are mediated by its principal receptors VEGFR1 and VEGFR2. The latter is primarily responsible for the mitogenic and angiogenic effects of VEGF [14]. Once VEGF binds to VEGFR2 it results in receptor dimerization, tyrosine kinase phosphorylation and subsequent activation of signaling pathways in endothelial cells that results in cell proliferation and migration. Thus inhibition of VEGF compromises the blood supply of tumors by causing regression in the scaffolding of immature blood vessels supplying the tumor. Xenograft models of lung cancer have also shown that VEGF inhibition can result in increased apoptosis of tumor cells [15]. Based on the understanding of the basic biology of VEGF, attempts have been made to use it as a target to inhibit angiogenesis.

bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody against VEGF that has been approved in the US and Europe for first-line treatment of advanced nonsquamous NSCLC. The Eastern Cooperative Oncology Group (ECOG) trial 4599 was a phase III trial involving 878 treatment-naïve

patients with advanced nonsquamous NSCLC who were randomized to receive carboplatin (AUC 6) plus paclitaxel 200 mg/m^2 with or without bevacizumab (15 mg/kg) every three weeks for six cycles [16]. After the initial phase, patients received bevacizumab monotherapy at the same dose every three weeks until disease progression or development of intolerable toxicity. Median overall survival (OS), progression free survival (PFS) and response rates (RR) were higher in the bevacizumab arm (OS 12.5 versus 10.2 months P = 0.007; PFS 6.4 versus 4.5 months $P < 0.001$; RR 27.2% verus 10% $P < 0.001$). There was a slightly higher risk of development of hemorrhage, grade 3–4 hypertension and grade 4–5 neutropenia in the bevacizumab arm. Another large phase III trial of cisplatin plus gemcitabine with or without bevacizumab in the first-line setting in patients with advanced nonsquamous NSCLC (AVAiL) recruited 1044 patients randomized to three arms [14]. The dose of bevacizumab used was 7.5 mg/kg or 15 mg/kg every three weeks. Preliminary results show that the response rates, and PFS were higher in the bevacizumab arm (RR 20% without bevacizumab, 34% with low-dose bevacizumab and 30% with high-dose bevacizumab; Median PFS 6.1 months without bevacizumab, 6.7 months with low-dose bevacizumab and 6.5 months with high-dose bevacizumab). There was a statistically significant reduction in the risk of relapse in those patients who received bevacizumab with chemotherapy (HR 0.75 $P < 0.002625$ in the low-dose arm and HR 0.82 $P < 0.0301$ in the high–dose arm). As was seen in ECOG 4599, treatment with bevacizumab was associated with a slightly higher incidence of grade 4–5 neutropenia, grade 3–4 hypertension and development of hemorrhage.

VEGF–Trap

VEGF–Trap is a fusion product of domains from VEGFR1 and VEGFR2 with the Fc portion of immunoglobulin G [17]. A phase II study of VEGF–Trap in patients with advanced NSCLC who were resistant or refractory to platinum-based chemotherapy and erlotinib showed a partial response (PR) rate of 3.7% and 67% stable disease (SD) maintained over 60 days when the molecule was given at a dose of 4 mg/kg every 2 weeks [14]. At present a phase III trial (EFC10261) of VEGF–Trap in the second-line setting in patients with advanced or metastatic NSCLC is ongoing. Patients receive docetaxel at a dose of 75 mg/m^2 administered intravenously on day 1 with or without VEGF–Trap (Aflibercept 6 mg/kg) also administered on day 1, every 3 weeks until disease progression or death [14].

AZD2171

AZD2171 is an orally administered inhibitor of VEGFR, particularly VEGFR2. In a phase I study with carboplatin and paclitaxel in patients with advanced NSCLC, AZD2171 was found to be reasonably well tolerated and a response rate of 45% was observed [18]. A dose of 30 mg per day was recommended for further studies. The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) has evaluated the combination of AZD2171 with carboplatin and paclitaxel in a randomized phase II/III trial as first-line therapy

of NSCLC. It was recently decided not to continue into phase III following the planned end of phase II efficacy and tolerability analysis by the study's Data Safety Monitoring Committee since the targeted progression free survival was not met.

dual targeting of VEGF and EGFR pathways

Combined blockade of the VEGF and EGFR pathways has shown to have additive antitumor activity in pre-clinical studies. Hence clinical trials have been designed to explore this approach in treatment of NSCLC.

A randomized phase II trial studied the combination of bevacizumab and erlotinib in patients with recurrent or refractory NSCLC [19]. The combination was compared to chemotherapy alone (docetaxel 75 mg/m^2 or pemetrexed 500 mg /m^2) or chemotherapy plus bevacizumab. The combination of bevacizumab and erlotinib compared favorably with the other two arms (median PFS 4.4 months versus 4.8 months versus 3 months, median survival 13.7 months versus. 12.6 months versus 8.6 months respectively) with a reasonable toxicity profile. It appears that a combination of two targeted agents may be as effective as, or more effective than, chemotherapy in pretreated patients with advanced NSCLC. Other phase II studies evaluating the combination of bevacizumab and erlotinib are ongoing in the first-line setting [14]. Large randomized studies are underway in which the combination of bevacizumab and erlotinib forms one of the treatment arms include the ATLAS trial (bevacizumab with or without erlotinib until disease progression in patients with advanced or metastatic NSCLC who have achieved PR or SD after four cycles of platinum doublet chemotherapy) and the BeTa trial (bevacizumab with or without erlotinib in the second-line treatment of advanced or metastatic NSCLC) [14].

ZD6474

ZD6474 is a dual kinase inhibitor that blocks VEGF2, VEGF3 and EGFR. In preclinical studies it has shown activity in the A549, Calu-6 and PC-9 lung cancer xenograft models [20, 21]. A number of phase III trials are evaluating the role of ZD6474 in advanced NSCLC [14]. These studies include a phase III trial of ZD6474 plus docetaxel versus docetaxel in the second-line setting after failure of one chemotherapy regimen, and a phase III trial comparing ZD6474 to erlotinib after failure of up to two prior regimen. In addition a randomized phase II trial is evaluating the combination of carboplatin plus paclitaxel plus ZD6474 against carboplatin plus paclitaxel in the first-line treatment of patients with advanced NSCLC. The drug has shown activity as a single agent and in combination with chemotherapy in several studies.

XL647

XL647 is an inhibitor of EGFR, VEGFR2, ErbB2, and EphB4 that is currently undergoing a phase II open-label, non-randomized study in patients with previously untreated advanced NSCLC [14].

other VEGFR kinase inhibitors

Two multitarget TKIs that are undergoing clinical trials in NSCLC are sorafenib tosylate and sunitinib malate.

sorafenib

Sorafenib targets Raf-1, VEGFR2, VEGFR3, Flt-3, c-Kit and platelet-derived growth factor receptor (PDGFR)-b [22]. In a phase II trial in 52 patients with advanced NSCLC treated with sorafenib at a dose of 400 mg per day, 59% patients achieved SD but no confirmed PRs. A PFS of 11.9 weeks and OS of 29.3 weeks were seen [23]. Phase III trials evaluating sorafenib in patients with advanced NSCLC include one comparing carboplatin plus paclitaxel with or without sorafenib and another comparing cisplatin plus gemcitabine with or without sorafenib [14]. The former study has been recently terminated after an interim analysis determined futility, and in this analysis patients with squamous histology had a markedly higher risk of early death. The latter study is still accruing.

sunitinib

Sunitinib has activity against VEGFR1, VEGFR2, VEGFR3, Flt-3, PDGFR-a, PDGFR-b and c-Kit. It has shown activity in preclinical studies in lung cancer models [24, 25]. In a phase II trial Brahmer et al. reported PR of 2% and PFS of 12.1 weeks with sunitinib monotherapy in previously treated patients with metastatic disease [26]. Socinski et al. recently reported results of another phase II trial of sunitinib in patients with advanced NSCLC [27]. Sunitinib was administered at a dose of 50 mg per day for 4 weeks of a 6-week treatment cycle in patients who had failed previously administered platinum-based chemotherapy. A total of 63 patients were treated. Seven PRs were noted for an objective response rate of 11.1%. Another 18 patients (28.6%) exhibited stable disease. The median PFS was 12 weeks and median OS was 23.4 weeks. Another phase II study is evaluating the role of consolidation therapy with sunitinib in patients with locally advanced or metastatic NSCLC who have completed first-line chemotherapy with carboplatin plus paclitaxel (NCT00113516). The combination of sunitinib at a dose of 37.5 mg per day and erlotinib at a dose of 150 mg per day is being evaluated in a randomized phase III trial in patients who have been previously treated with a platinum-based regimen (NCT00457392).

targeting multiple pathways in NSCLC

As we become more aware of the molecular aberrations that result in lung cancer, it is becoming increasingly clear that targeting a single biologic pathway is of limited value since most tumors bypass the therapeutic blockade by using other pathways to ensure cellular proliferation, angiogenesis and survival. In this context it becomes critically important to identify potential biologic targets, the blockade of which would affect multiple downstream signaling cascades, thereby increasing the anti-cancer action of the therapeutic maneuver. The following examples illustrate this concept.

Src and lung cancer

The Src family of tyrosine kinases transduce signals from cell surface proteins to intracellular proteins as well as transcription factors [28]. Under physiologic conditions Src is present in an inactive phosphorylated state. Aberrant activation of Src by dephosphorylation leads to cell proliferation and migration. Increased Src activity has been reported in 60–80% of adenocarcinomas and bronchoalveolar carcinomas of the lung and about 50% of squamous cell lung cancers [29]. Src serves as a mediator for the activation of a number of pathways essential for tumorigenesis [reviewed in reference 30]. Among these pathways, is the signal transducer and activator of transcription (STAT)-3, which is activated by epidermal growth factor, interleukin 6 and hepatocyte-derived growth factor. Src also activates the VEGF pathway via STAT-3. In addition activation of Src in human lung cancer cells is associated with inhibition of anoikis. Animal experiments have shown that Src and EGFR tend to act synergistically [31]. Therefore it is not surprising that inhibition of Src kinases in EGFR-dependent NSCLC cell lines results in inhibition of EGFR-dependent pathways ultimately leading to apoptosis [32]. Src may also be involved in EGFR resistance. One mechanism of resistance to EGFR could involve activation of other Src-mediated pathways such as P-AKT and ERK [33]. Another mechanism of resistance to EGFR TKIs involves loss of E-cadherin expression caused by Src activation. Preclinical studies have shown that restoration of E-cadherin expression in lung cancer cell lines leads to increased sensitivity to EGFR TKIs [34].

Among the Src inhibitors undergoing phase I clinical trials are AZD0530 and SKI-606 (bosutinib). Dasatinib is a multitarget inhibitor of Src kinases, Bcr-Abl, Kit, PDGFR-b and Eph receptors that has been successfully used in Philadelphia chromosome-positive chronic myelogenous leukemia and acute lymphoblastic leukemia [35]. In preclinical studies, NSCLC cells treated with dasatinib showed decreased cell growth and invasive potential, and in EGFR-dependant cell lines it also induced apoptosis [32, 36]. Dasatinib is currently undergoing phase II trials in NSCLC.

heat shock protein 90 inhibition in lung cancer

Heat shock protein 90 (Hsp90) has been described as a molecular chaperone that plays an important role in the refolding of denatured proteins, and promotes conformational maturation and stabilization of its client proteins, many of which play a critical role in tumor formation and survival [37]. These client proteins include EGFR, HER2, Raf-1, Akt, and mutated p53, among several others [38]. Preclinical studies have shown increased expression of Hsp90 in lung cancer cell lines. Hsp90 inhibitors such as geldanamycin (GA) and 17-allylaminogeldanamycin (17-AAG) exhibit inhibition of growth and induce a G2/M phase arrest in the A549 and H226B lung cancer cell lines. In addition a combination of 17-AAG and radiation had an additive effect on inhibition of cell growth [37]. Gene dosage and expression analysis of 32 tumor samples from patients with stage I and II NSCLC who had undergone radical resection showed a deletion on 14q32.2-33 in 44% cases [39]. There were 109 genes that mapped to this

region on chromosome 14 but the only gene that showed a significant reduction in expression in patients harboring the deletion was the one that encoded for the Hsp90 protein. Also of interest, in the group of 29 patients who were included in survival analysis, deletion on 14q32.2-33 correlated with better overall survival (5 year OS 69% versus 41%, $P = 0.004$). Based on this data, Hsp90 inhibition can be developed as a treatment option in lung cancer.

In xenograft models 17-AAG has been shown to down-regulate expression of wild-type and mutant EGFR [40]. It has also been shown that 17-AAG can be safely coadministered with paclitaxel. Various Hsp90 inhibitors that are currently being evaluated in clinical trials are summarized in Table 1.

epigenetic alterations in lung cancer

Epigenetic changes refer to those molecular mechanisms that can alter gene expression without an actual change in the DNA sequence. Important epigenetic changes that have been described in lung cancer include hypermethylation of promoter regions of tumor suppressor genes and histone deacetylation. Both these mechanisms lead to inhibition of tumor suppressor gene expression.

Hypermethylation of CpG islands in the promoter regions of tumor suppressor genes is associated with loss of gene expression, which contributes to the malignant phenotype. Most lung tumors are known to harbor multiple genes with aberrant promoter methylation [41]. Inhibitors of DNA methylation can reverse loss of gene expression associated with promoter hypermethylation. Thus the hypermethylated promoter regions of affected genes form a novel target for drug development. Azacytidine, an inhibitor of DNA hypermethylation has shown clinical benefit in myelodysplastic syndromes. However, the role of inhibitors of aberrant promoter methylation in lung cancer needs further evaluation.

Histone acetylation and deacetylation play important roles in chromatin remodeling, which in turn regulates gene expression. Acetylation of key lysine residues on histones leads to an 'open' chromatin structure. Consequently transcription factors can access their target sequences resulting

in increased gene expression. Deacetylation of lysine residues results in the converse phenomenon leading to 'closed' chromatin where transcription factors cannot access their target sequences leading to decreased gene expression [42]. Histone deacetylase (HDAC) inhibitors can induce cell differentiation and apoptosis. The HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) has been shown to inhibit the growth of the lung cancer cell lines NCI-H520, NCI-H460, NCI-H522, NCI-H1299 and SK-MES-1 [42]. Treatment with SAHA is also associated with up-regulation of the cyclin-dependent kinase inhibitor p21^{WAF1}, increased levels of p53 and decreased expression of c-myc and the anti-apoptotic protein bcl-2 [42]. Since SAHA showed anti-proliferative activity in lung cancer cell lines it is now being investigated as a novel targeted therapy in the clinical setting (Table 2).

The biological role of class II histone deacetylases serves as another illustration of the close relationship between different biologic pathways in the development of malignancy. Some HDAC inhibitors act at a non–transcriptional level by inhibition of HDAC6/Hsp90 complexes. It has been shown that HDAC inhibitors like SAHA inhibit class II HDACs leading to depletion of VEGFR proteins via Hsp-mediated proteasomal degradation [43].

the role of telomerase in lung cancer

Telomeres are present at the ends of mammalian chromosomes and are responsible for protecting them from degradation. However they shorten after each round of cell division. Telomerase plays a critical role by elongating telomeric DNA thus ensuring chromosomal stability. Increased activity of telomerase is seen in a variety of human cancers. About 80% of NSCLCs and 100% of small cell lung cancers show increased telomerase activity [44]. The telomerase template antagonist GRN163L has been shown to inhibit growth of lung cancer xenografts [45]. It also inhibits anchorage-independent growth. GRN163L is currently undergoing a phase I study in combination with paclitaxel and carboplatin in patients with advanced or metastatic NSCLC (NCT00510445; Geron Corporation).

Table 1. Hsp90 Inhibitors in Clinical Trials

Phase of Trial	Drug	Tumor type	Sponsor	ClinicalTrials.gov Identifier
I	SNX–5422 Mesylate	Refractory solid tumors	Serenex, Inc.	NCT00506805
I	SNX–5422 Mesylate	Refractory solid tumors/lymphomas	National Cancer Institute (NCI)	NCT00644072
II	IPI–504	Metastatic melanoma	MedImmune LLC	NCT00627419
II	IPI–504	HER2+ breast cancer	MedImmune LLC	NCT00627627
I/II	IPI–504	Relapsed/refractory stage IIIb/IV NSCLC	Infinity Pharmaceuticals	NCT00431015
II	IPI–504	Hormone-resistant prostate cancer	Infinity Pharmaceuticals	NCT00564928
I	CNF2024 (BIIB021)	Advanced solid tumors	Biogen Idec	NCT00345189
II	Tanespimycin	Pancreatic cancer	Mayo ClinicNCI	NCT00577889
III	Tanespimycin(KOS–953)	Multiple myeloma in first relapse	Kosan Biosciences	NCT00546780
I/II	AUY922	Advanced solid tumors	Novartis	NCT00526045
I	STA9090	Solid tumors	Synta	–

Table 2. Selected clinical trials of SAHA (Vorinostat/MK0683) in NSCLC

Phase	Sponsor	ClinicalTrials.gov identifier	Comments
I	Merck	NCT00423449	Vorinostat used with gemcitabine plus paclitaxel in patients with advanced NSCLC
II	University of Wisconsin, Madison, National Cancer Institute (NCI)	NCT00138203	SAHA used in patients with relapsed NSCLC
			This study was completed in December 2007
I/II	Spanish Lung Cancer Group	NCT00503971	Vorinostat used in combination with erlotinib in NSCLC patients with EGFR mutations and disease progression after erlotinib treatment
II	California Cancer Consortium, National Cancer Institute (NCI)	NCT00481078	Carboplatin and Paclitaxel with or without Vorinostat in treating patients with stage III or stage IV NSCLC
II/III	Merck	NCT00473889	Paclitaxel plus Carboplatin with Vorinostat or Placebo in patients with Stage IIIB (with pleural effusion) or Stage IV NSCLC

RAS mutations and the role of c-Met in lung cancer

RAS protooncogenes encode G-proteins that regulate signal-transduction pathways involved in cell proliferation and survival. A total of 10–15% of NSCLCs harbor RAS mutations, the vast majority of which are KRAS mutations [reviewed in reference 2]. These mutations are present in 30% of adenocarcinoma histologies. In contrast to EGFR mutations that are seen more commonly in non-smokers, KRAS mutations are seen mainly in smokers. In a study of 73 patients with NSCLC treated with EGFR TKIs, Massarelli et al. showed that KRAS mutations were present in 16 of 70 (22.8%) patients [46]. Further, the presence of KRAS mutations correlated with progressive disease and shorter median time to progression. Presence of activating RAS mutations seemed to overcome the favorable effect of increased EGFR copy number in predicting response to EGFR TKIs.

c-Met is yet another membrane bound tyrosine kinase which is important in lung cnacer. The binding of c-Met to its ligand, hepatocyte growth factor (HGF) results in the activation of multiple signaling cascades resulting in cell proliferation and survival. It has also been shown that c-Met also plays a role in tumor angiogenesis. Not surprisingly c-Met has also been implicated in the development of resistance to EGFR TKIs [9]. Amplification of cMet has been shown to be the cause of resistance in gefitinib resistant cell lines. Preclinical studies have shown that the c-Met inhibitor PHA-665752 induces apoptosis in lung adenocarcinoma cell lines as well as endothelial cells within tumors [47]. In addition to PHA-665752, various other strategies to inhibit c-Met are in the process of development. It will be interesting to see if combined c-Met plus EGFR inhibition can be developed as a viable therapeutic strategy.

insulin-like growth factor 1 and lung cancer

Binding of insulin-like growth factor 1 (IGF-1) to its receptor (IGF-1R) plays an important role in cell proliferation and differentiation by activation of the RAS-mitogen-activated protein kinase (MAPK) and phopsphatidylinositol-3 kinase (PI-3K)-AKT pathways [48]. IGF-1 and IGF-1R expression is increased in lung cancer. Studies have also shown that the IGF-1 and EGFR pathways are closely associated. Phosphorylation of insulin receptor substrate-1 (IRS-1) by IGF-1R leads to stimulation of the PI3K and STAT pathways. Cross-talk between the EGFR and IGF-1R pathway is yet another way by which resistance to EGFR TKIs can develop. IGF-1R inhibitors are currently in the process of development. Initial results of a phase II trial evaluating the efficacy of the IGF1-R antibody CP-751871 in combination with carboplatin and paclitaxel as first-line treatment of advanced NSCLC was reported at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2007 [49]. Patients with stage IIIB or IV NSCLC with good performance status (ECOG PS 0 or 1) were randomized to receive carboplatin (AUC6) and paclitaxel (200 mg/m^2) with or without CP-751871 (10 mg/kg) every three weeks for up to 6 cycles. A response rate of 46% was seen in the study group compared to 32% in the chemotherapy-alone arm. The response rate in the study arm was even higher (52%) in those patients who did not have adenocarcinomas. The combination was well tolerated and major adverse effects (study arm versus chemotherapy-alone arm) included hyperglycemia (20% versus 10%), fatigue (15% versus 8%), neutropenia (13% versus 20%) and neuropathy (10% versus 4%). Some of the other studies involving CP-751871 that are ongoing are tabulated in Table 3. A decision has recently been made to further this antibody to phase III trial in combination with carboplatin–paclitaxel.

other novel concepts in targeted therapy of lung cancer

targeting apoptotic pathways in lung cancer

Reactivation of death receptor signaling has been postulated as a novel approach to treat lung cancer. Induction of tumor necrosis factor-related apoptosis inducing ligand (TRAIL) with or without chemotherapy or radiation therapy is being considered as a treatment option. Agonistic TRAIL receptor

Table 3. Anti-IGF-1R-based therapy in NSCLC

Phase	Sponsor	ClinicalTrials.gov identifier	Comments
I	Pfizer	NCT00603538	CP-751871 plus carboplatin plus paclitaxel
I	Pfizer	NCT00560573	CP-751871 plus cisplatin plus gemcitabine
III	Pfizer	NCT00596830	Carboplatin and Paclitaxel with or without CP-751871

monoclonal antibodies are also being evaluated in preclinical studies [reviewed in reference 50]. It has been shown that bortezomib sensitizes NSCLC cells to recombinant human TRAIL (rhTRAIL) by caspase-8 and caspase-9-mediated apoptosis [51]. Therefore combination of bortezomib and rhTRAIL can also be explored as a novel treatment strategy against NSCLC.

cancer vaccines

Immunotherapy has been explored as treatment modality for melanoma, renal cell carcinoma and several other solid tumors. However, developing vaccines against lung cancer has been challenging given its relative tolerance to immune-based therapies [52]. Tumor infiltrating lymphocytes in lung cancers are usually immunosuppressive T regulatory cells that inhibit autologous T cell proliferation. Nevertheless recent work has focused on enhancing tumor antigen recognition. Belagenpumatucel-L (NCT00641966), a TGF Beta-2 antisense gene-modified allogeneic tumor cell vaccine is being evaluated in a phase III trial. Other vaccines that are undergoing development in NSCLC include MAGE-3 (phase III in the adjuvant setting), GVAX, B7.1, EP2101, BLP-25 (phase III study in locally advanced NSCLC), L523S and telomerase GV1001.

conclusions

Over the last few years we have come a long way in understanding the complex molecular alterations that are responsible for the development of lung cancer. Harnessing this knowledge in the development of newer treatment strategies is imperative since clinical outcomes in advanced lung cancer with cytotoxic chemotherapy and radiation therapy remain modest at best. An understanding of the role of the EGFR and VEGF pathways has already resulted in the development of specific therapies targeting these pathways. However, the close association of these pathways with a number of other signaling cascades results in the development of resistance to targeted therapies that are in use today. Hopefully, with better recognition of the molecular pathogenesis of lung cancer, specific inhibitors will be developed which can be used with currently available treatment modalities to create truly targeted therapies in the future.

disclosures

No significant relationships.

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