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Review Article

Targeted Therapy Advances in Metastatic Non Small Cell Lung Carcinoma

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Abstract

Non Small Cell Lung Carcinoma (NSCLC) remains a major health burden worldwide; it is the leading cause of cancer death in the world. In the last decade, stereotypical treatment has given way to the concept of personalized medicine, by a better understanding of molecular features that plays a role in cancer apparition. Actually, the identification of molecular abnormalities leads to targeted therapies that improve the therapeutic outcome in this disease. Epidermal Growth Factor Receptor (EGFR) inhibitors, Anaplastic Lymphoma receptor tyrosine Kinase (ALK) inhibitors and antiangiogenic therapies are already approved and are of current use. Moreover, we know more about the mechanisms of resistances to a first line treatment. Other new molecules of second and third generation are emerging and getting rapidly approved by medical authorities. The new approach of immunotherapy in NSCLC makes the therapeutic panel large. In this review, we will put the item on oncogenetic characteristics of NSCLC as well as new targeted therapies including anti EGFR anti ALK agents, antiangiogenic therapies and immune checkpoints inhibitors.

Introduction

Lung cancer is the leading cause of cancer death in the world. Indeed, the majority of patients are diagnosed at an advanced stage. Several years already, stereotypical treatment has given way to the concept of personalized medicine. Treatments are adapted to molecular alterations of tumor signaling pathways. Too recently a better knowledge of molecular biology supported major therapeutic advances that were performed in patients with known driver oncogenes; by a better control of the phenomena of resistance, and also in those who do not have genetic mutations through the successful emergence of immunotherapy in Non Small Cell Lung Carcinoma (NSCLC).

Molecular Aberrations

The identification of oncogene drivers in NSCLC subdivides the disease in multiple molecular subgroups and lead to a real treatment card. The first known molecular aberrations are Epidermal Growth Factor Receptor (EGFR) mutations and then Anaplastic Lymphoma Kinase (ALK) rearrangements.

The most common EGFR mutations are deletions within exon 19 with a variation of 9-18 nucleotides, and a point mutation at exon 21 (L858R). Other less common mutations are in exon 18, and insertions in exon 20. EGFR-activating mutations are predictive for improved sensitivity and outcomes with EGFR-targeted tyrosine kinase inhibitors TKIs [1]. However, therapeutic resistance occurs due to acquired mutations, the best known is T790M which is most frequently associated with previous TKI treatment. This type of mutation inhibits or reverses the binding of the TKIs gefitinib and erlotinib and prevents the receptor blockade. Anaplastic Lymphoma Kinase (ALK) rearrangements are predictive for improved sensitivity and outcomes with ALK targeted TKIs [2]. Here again, resistance occurs in about one year of treatment, the best known are the C1156Y and L1196M [3].

Beyond EGFR mutations and ALK rearrangements, several new targetable oncogenes testing are recommended in current practice such as ROS1, RET, BRAF, KRAS, HER2, (Table 1). These new oncogenes are of low frequency in NSCLC, in total they are found in 9% to 14% of lung adenocarcinomas and 16% to 30% of squamous cell lung carcinomas [4], but they could potentially be targeted with drugs already approved for other localizations or with investigational agents [5].

In the recent last years, we understood better the concept of immunosurveillance and the reasons of the failure of immune system to recognize tumor antigens and to generate spontaneous antitumoral response. This led to the identification of targetable immune checkpoint, as the programmed cell death protein1 (PD-1), in several malignancies including lung carcinomas [6]. The emergence of Immunotherapy has extended the therapeutic panel of NSCLC, especially because the immune checkpoint inhibitors are of impressive clinical activity, durable responses and a favorable toxicity profile.

New Options for Patients with EGFR Abnormalities

Tyrosine kinase inhibitors

Compared to chemotherapy, EGFR Tyrosine Kinase Inhibitors (TKIs) have shown a benefit in progression free survival, they represent actually a standard of care in the treatment of NSCLC with EGFR mutation.

Erlotinib, Gefitinb which are TKIs of first generation and Afatinib; an irreversible anti EGFR TKI are approved by the Food and Drug Administration(FDA) in patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 substitution in the first line setting . Unfortunately, nearly two-thirds of patients treated with

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Table 1: Prevalence and clinical features of molecular abnormalities in NSCLC.

Molecular abnormality	prevalence	Clinical features
EGFR mutations	10% to 15% patients 50% of Asian population[1]	Caucasian population Adenocarcinoma Never or light smokers Female patients
ALK rearrangements	2 to 7% of NSCLC	Never or light smoker Almost young men Mutually exclusive with EGFR mutation[2]
BRAF mutation	2%(20)	Never or light smokers [7]
MET gene amplification	about 2-4% of lung adenocarcinoma lower rates in squamous carcinomas [8]	Frequently present in patients with resistance to EGFR inhibitors
ROS gene rearrangements	1 to 6%	Never or light smoker Mutually exclusive with EGFR
RET gene rearrangements	2%	Never or light smoker Mutually exclusive with other driver oncogenes young patients poorly differentiated
PD-L1 expression	Nearly 60% of NSCLC [6]	_
KRAS mutation	about 20%–25% of lung adenocarcinoma 4% of lung squamous cell carcinoma [9]	More frequent in smokers Low frequency in Asian population Mutually exclusive with other molecular aberrations [9]
PIK3CA	2% of NSCLC More frequent in squamous cell carcinoma [4]	Occurs in combination with other coexisting abnormalities [4]
HER2 strong over expression	2% -4 % of NSCLC More prevalent in adenocarcinoma [10]	_

EGFR TKI therapy acquire resistance related to the T790M mutation. Until recent years, treatment options after relapse were limited and the use of chemotherapy was the only therapeutic choice [7-10].

Rociletinib (CO-1686) is an oral, irreversible inhibitor of both activating EGFR mutations and T790M mutation [11]. It received Breakthrough Therapy designation from the FDA in May 2014. Rociletinib was tested in a phase 1-2 study in patients with EGFR-mutated NSCLC who had progressed during previous treatment with an EGFR inhibitor [12]. It demonstrated potent activity in case of T790 mutation with an objective response rate of 59% versus 29% when EGFR T790 was negative, efficacy was consistently observed at the dose of 900mg twice daily in continuous 21-day cycles. The only dose-limiting adverse event was hyperglycemia.

Osimertinib (AZD9291) is another third generation EGFR inhibitor, active in patients with T790 mutations. It was tested in two Phase II studies and demonstrated efficacy in patients with EGFR T790M NSCLC who had progressed on or after an EGFR-TKI with an objective response rate of 66%, and a Progression-Free Survival (PFS) of 9.7 months [13]. Osimertinib was approved by the food and drug administration in November 2015. On February 2016, the European Commission (EC) has granted conditional marketing authorization for Osimertinib at the posology of 80mg once-daily for the treatment of adult patients with locally advanced or metastatic Epidermal Growth Factor Receptor (EGFR) T790M mutation-positive NSCLC.

Afatinib is an additional option after failure of a first line treatment with a manageable safety profile. The open –label phase III Lux-Lung 8 study showed that Afatinib improves progression free survival and overall survival compared to erlotinib in the second line setting [14]. It seems that it is also active in patients who develop the T790 mutation [15], but actual data is not enough to prove it.

Monoclonal antibodies

Monoclonal antibodies anti EGFR (mAbs) target the extra-cellular domain of EGFR and block its activation.

In the phase III Flex trial, Cetuximab, an anti EGFR monoclonal antibody, combined to chemotherapy improved slightly but significantly the overall survival of patients with advanced unselected NSCLC [16]. This small benefit was seen regardless of histological type. The subgroup analysis found that high EGFR expression according to a tumour IHC score of 200 may be a predictive biomarker for a treatment benefit [17]. This data should be confirmed in a prospective trial. Cetuximab is not approved by FDA and EMA in NSCLC.

Necitumumab (IMC-11F8) is a recombinant IgG1 human monoclonal antibody designed to bind and block the ligand binding site of EGFR. It showed a potent activity in the phase III Squire Trial in combination with gemcitabine and cisplatine. This association led to a significant gain in overall all survival [18]. It is the only anti EGFR approved in squamous NSCLC.

New Options for Patients with ALK and ROS1 Rearrangements

NSCLC population with positive ALK rearrangement has a prolonged PFS with Crizotinib; the first generation ALK and ROS1 inhibitor; compared to standard platinum based chemotherapy. Currently, Crisotinib is recommended in the first line therapy when ALK rearrangement is identified, it is approved by FDA and by EMA.

Crizotinib is also the first and only FDA-approved biomarker-driven therapy for ROS1-positive metastatic NSCLC. This recent approval, March 2016, is based on a multicenter, single-arm Phase 1 study, the ROS1 cohort of Trial PROFILE 1001, that included 50 patients with ROS1-positive metastatic NSCLC treated with Crizotinib. Objective response rate was of 66 percent and the median duration of response was 18.3 months [19].

Despite this targeted therapy, progression occurs in the large majority of patients, due to a poor activity of Crizotinib in Central Nervous System (CNS) and development of secondary resistance.

Secondary resistance to Crizotinib may be due to ALK dominant point mutations, the most described until now are the C1156Y and

L1196M[3], or may be explained by activation of other signalization pathways such as activation of IGF-R, amplification of MET; KIT or EGFR and KRAS mutation.

Ceritinib is a second generation ALK inhibitor, has demonstrated promising results in the dose-escalation Ascend-1 Phase I trial, which tested Ceritinib in a population of ALK-positive, NSCLC who had progressed on or were intolerant to crizotinib. Ceritinib was administrated at the dose of 400mg to 750mg once daily. The objective response rate was 56% after previous treatment by crizotinib, interestingly patients with brain metastasis had an overall cranial response rate of 50% [20]. On April, 2014, the FDA approved ceritinib for the treatment of patients with Anaplastic Lymphoma Kinase (ALK)-positive, metastatic Non-Small Cell Lung Cancer (NSCLC) with disease progression on or who are intolerant to Crizotinib [21]. The major toxicities of Ceritinib were diarrhea, vomiting, dehydration and elevated aminotransferase levels.

Alectinib is another second generation ALK inhibitor, active against L1196M mutation. It was tested in two trials, the north American phase II study [22] and the Global phase II study [23], at the dose of 300mg twice daily in patients treated for NSCLC with ALK rearrangement after failure of crizotinib, it has induced an objective response rate of 48% and 50% respectively and a median duration of response of 7, 2 months and 11, 2 months respectively. Moreover, those studies attested that Alectinib is active on CNS. The drug is well tolerated and is now FDA-approved for the treatment of metastatic ALK+ NSCLC after progression or in tolerated crizotinib.

Brigatinib is also a second generation ALK inhibitor; it overcomes L1196M ALK mutation and EGFR T790M mutation. In a phase I/II single-arm, multicenter study in patients with advanced malignancies [24], brigatinib showed an efficacy among the 79 patients ALK+ NSCLC pts and permitted a progression free survival of 47weeks when patients were treated first by crizotinib, it demonstrated a clear activity in CNS.

Recent studies are testing a third generation ALK inhibitor: Lorlatinib which is potent against all known resistant mutants and inhibits ALK, ROS1.Lorlatinib is active after failure of first and second generation ALK inhibitor, The L1198F substitution confers resistance to lorlatinib, However, L1198F paradoxically enhances binding to crizotinib, negating the effect of C1156Y and desensitizing resistant cancers to crizotinib [25].

Immune Checkpoint Inhibitors

Nivolumab is a genetically engineered, fully human immunoglobulin IgG4 monoclonal antibody specific for human programmed death-1 (PD-1) [26].

In the phase III trial CheckMate 057, Nivolumab showed a significant benefit in overall survival versus docetaxel 75mg/m^2 in unselected patients with advanced, previously treated nonsquamous NSCLC, nevertheless PD-L1 expression is strongly predictive for clinical outcome and all efficacy end points [27].

Nivolumab was also tested in squamous NSCLC. Thus, the phase III trial Checkmate 017 compared nivolumab versus docetaxel in patients with advanced NSCLC after one prior platinum-containing regimen [28]. Overall survival was significantly longer with nivolumab than with docetaxel. The risk of death was 41% lower with nivolumab but PD-L1 expression was neither prognostic nor predictive of any of the efficacy end points.

In the two studies, adverse events severity was lower in the nivolumab group than in the docetaxel group, and pneumonitis; which occurred in nearly 1% of patients; was the most adverse event which led to discontinuation of treatment.

Pembrolizumab is another anti PD1 approved in the second line treatment of NSCLC, only for patients whose tumors express PD-L1 on at least 1%, indeed this population may get a survival benefit from Pembrolizumab as demonstrated by the Keynote -010 trials [29].

Advances on immunotherapy are interesting and the approval of Atezolizumab, a monoclonal anti body that binds programmed cell death -1 ligand, when the tumor express PD-L1, offer an additional treatment option in the second line setting. In the phase II randomized Poplar study [30]. Atezolizumab improved significantly the objective response rate, progression free survival and overall survival correlation with increasing PD-L1 expression.

Several other PD-1/PD-L1 inhibitors are being studied, as Durvalumab and Avelumab. The future of immunotherapy seems to be in favor of combinations between immune checkpoints inhibitors binding different targets, such as the association of Nivolumab and ipilimumab or between immunotherapy and chemotherapy.

Antiangiogenic Therapy

Angiogenesis plays a central role in the tumor growth and metastatic dissemination. For many years already, Bevacizumab is approved for the treatment of patients with advanced non squamous NSCLC.

Nintedanib is a triple angio kinase inhibitor that blocks simultaneously the proangiogenic pathways mediated by Vascular Endothelial Growth Factor Receptors (VEGFRs), Platelet-Derived Growth Factor Receptors (PDGFRs) and Fibroblast Growth Factor Receptors (FGFRs). In the phase III LUME-Lung 1 study which evaluated the combination of Nintedanib with docetaxel versus docetaxel with placebo, the Nintedanib association significantly prolonged Progression-Free Survival (PFS). There was a significant improvement in overall survival only among patients with adenocarcinoma, especially those who had a rapidly progressive disease [31]. Nintedanib is approved only in Europe in the treatment for advanced or metastatic Adenocarcinoma in the second line setting.

Ramucirumab is a fully human monoclonal antibody that binds the activity of Vascular Endothelial Growth-Factor Receptor 2 (VEGFR). Its FDA approval is based on the finding of the phase III Revel trial that compared ramucirumab plus docetaxel with placebo plus docetaxel in NSCLC patients who experienced disease progression after treatment with platinum-based chemotherapy for locally advanced or metastatic disease [32]. Ramucirumab associated to docetaxel improved significantly the overall survival, disease free survival and objective response rate. It is a valid option in the second line setting. The most common grade 3 and higher adverse events, reported more frequently in patients in the ramucirumab than in the placebo group, were neutropenia, febrile neutropenia, fatigue,

leukopenia, and hypertension. The addition of Ramucirumab did not impair the patient's quality of life [33]. It is a valid option in the second line setting of advanced NSCLC.

Conclusion

The use of personalized medicine in lung cancer by targeting the molecular alterations is changing the standards of care and providing an interesting clinical benefit. Other novel agents are being investigated in clinical trials.

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