

TARGETED THERAPIES IN NON-SMALL CELL LUNG CANCER: WHICH IMPLICATION IN ROUTINE PRACTICE

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Abstract

The better understanding of lung cancer biology leads to the development of new drugs, targeting specific pathways involving oncogenes, tumour suppressor genes, growth factors receptors or angiogenesis. We reviewed the most representative results of the research on targeted therapies in NSCLC, focusing on the trials having a direct implication in routine practice. In selected patients, targeted therapy may result in significant benefit with quite low toxicity. This is the case for EGF-R tyrosine kinase inhibitor (erlotinib and gefitinib), for antibodies directed to EGF-R (cetuximab) or VEGF (bevacizumab) and for crizotinib.

Key words: Non-small cell lung cancer, targeted therapy, gefitinib, erlotinib, tyrosine kinase inhibitor

INTRODUCTION

Randomised trials and meta-analyses have consistently shown that cisplatin-based chemotherapy improves survival in advanced non-small cell lung cancer (NSCLC) (1). Nevertheless, response and survival improvement are not uniform while toxicity can be substantial. The better understanding of lung cancer biology leads to the development of new drugs, targeting specific pathways involving oncogenes, tumour suppressor genes, growth factors receptors or angiogenesis. Multiple drivers' oncogenes are recognised. They are mainly, but not exclusively, associated with adenocarcinoma histology including mutations in the Kras, EGFR, PI3K, raf domains or the EML4-ALK gene fusion (2). In squamous cell carcinoma, key candidate genes are FGFR-1, SOX, MDM2, PDGFRA, MET... (3).

Through targeting a specific pathway and/or a specific population, new drugs have the potential of improved therapeutic index and selection of the patients benefiting most from this approach. Targeting therapies belong to different groups according to their mode of action. Drugs can act by blocking growth factors signalisation cascade (small inhibitor molecules

or monoclonal antibodies), by inhibiting angiogenesis (VEGF inhibitors, metalloproteinase inhibitors, COX-2 inhibitors...), or by inhibiting signal transduction (anti-sense oligonucleotides, farnesyltransferase inhibitors...).

The aim of this review is to present the most representative results of the research on targeted therapies in NSCLC, focusing on the trials having direct implication in routine practice. The review dwells essentially on phase III trials.

1) Blocking the signalisation cascade of growth factor receptors: the example of Epidermal Growth factor Receptor (EGFR)

a) Small inhibitor molecules

EGFR is the best example of the successful researches on targeted therapies. Gefitinib (ZD1839, Iressa®), and erlotinib (OSI-774, Tarceva®) are the first two molecules blocking the EGFR signalling pathway that are now commonly used in advanced NSCLC. These are tyrosine kinase inhibitors (TKI) that compete with ATP binding to the intracellular EGFR kinase domain.

Gefitinib, an anilinoquinazoline highly specific for EGFR and erlotinib, a quinazoline derivative, are both orally active and have been tested in first-line, singly or in combination with platinum-based chemotherapy, and for salvage therapy in advanced and metastatic NSCLC.

First line therapy

Two phase III trials tested the addition of gefitinib to chemotherapy (cisplatin -gemcitabine in INTACT I and carboplatin - paclitaxel in INTACT II) in chemonaive patients with advanced NSCLC (4, 5). The same design was performed for erlotinib in the TRIBUTE (carboplatin/paclitaxel +erlotinib or placebo) (6) and in the TALENT trials (cisplatin/gemcitabine + erlotinib or placebo) (7). In all studies, gefitinib and erlotinib were given for maintenance in non-progressing patients having received six cycles of chemotherapy plus the TKI. In none of the trials was a survival advantage demonstrated by adding TKI to conventional chemotherapy. However, when given as maintenance after four cycles of a platinum-based chemotherapy in non-progressing patients who did not receive a TKI in the induction phase, a survival improvement was noted (SATURN) (8). INFORM (a phase III, randomized, multicenter, parallel group study) investigated the efficacy, safety and tolerability of gefitinib (G) vs placebo (P) as maintenance therapy in Chinese patients with locally advanced/metastatic NSCLC following standard first-line platinum based chemotherapy. PFS was significantly longer with G compared with P (9).

The lack of effect of EGFR TKIs when added to chemotherapy being potentially related to a negative interaction at the time of chemotherapy administration, intercalation of EGFR TKI during chemotherapy was assessed in a phase III trial. This approach with erlotinib significantly prolonged progression free survival of patients treated with first line platinum based chemotherapy (10).

In contrast, sequential administration of platinum-doublet chemotherapy followed by gefitinib shows no overall benefit over continuous platinum- doublet chemotherapy, while an improvement in survival is suggested in adenocarcinomas (11).

These studies have been performed in unselected populations. However, it was shown that both TKI had a preferential activity in some subgroups: women, adenocarcinoma, nonsmoker, Asian ethnicity. When given front line in this enriched population, TKIs are effective in terms of response rate (RR) and progression free survival (PFS) (12). Mok et al. (12) randomly assigned previously untreated East Asian non smokers or former light smokers with advanced pulmonary adenocarci-

noma to receive gefitinib or carboplatin plus paclitaxel. Gefitinib proved to be superior, with improved RR and PFS, while survival rates were similar. Another important variable is the presence of an activating mutation of the EGFR gene, which is predictor of a better outcome with TKI. The 2 main locations are deletion in exon 19 and point mutation in exon 21 (13). Recently, 4 published studies showed that first line EGFR TKI (gefitinib or erlotinib) for patients harboring tumors with EGFR mutations improved progression-free survival, with acceptable toxicity, as compared with standard platinum-based chemotherapy (14-17). Survival was not improved, probably because of cross-over administration of the TKI in second line. Taking into account the presence of a mutation, the effect of ethnicity disappears, although the frequency of mutation is higher in Asia (30-40%) than in Caucasians (10%). Based on the data from 5 randomized trials, patients with activating EGFR mutation have to receive a TKI, either in first or second line. On the contrary, if the mutation status is unknown or if there is no mutation, giving a TKI in first line is associated with a deleterious effect in terms of RR, PFS and survival (TORCH study).

Could there be a place for TKI in first line treatment of locoregional disease? A phase III trial conducted in inoperable stage III NSCLC treated with concurrent chemoradiotherapy and docetaxel consolidation showed no benefit of gefitinib maintenance in tumours not progressing after induction therapy. Median survival time was 23 months in the gefitinib arm and 35 months in the placebo arm (18). Finally, a phase III randomized study showed that adjuvant gefitinib after complete resection of early stage NSCLC did not confer survival advantage in the overall population (19).

Salvage therapy

BR. 21 is the first placebo controlled randomised study showing that an oral EGFR TKI prolongs survival in stage IIIB or IV NSCLC, previously treated by one or 2 chemotherapy regimens. Patients received either erlotinib 150 mg per day or placebo until progression (20). Erlotinib showed progression-free and overall survival improvement (6.7 months vs 4.7 months). While survival differences were not statistically significant between gefitinib and placebo in the ISEL trial, the same trend favouring the TKI administration was observed (21). Both trials were performed in an unselected population. When looking at subgroups in the BR21 study (13), patients with EGFR increased gene copy number assessed by Fluorescent In Situ Hybridisation (FISH) analysis, non smokers and those presenting with adenocarcinoma had potentially more

advantage than the others to be treated with erlotinib. In second line, the INTEREST study established that gefitinib is not inferior to docetaxel, suggesting that gefitinib is a valid option for pretreated patients with advanced non-small-cell lung cancer (22). Nevertheless, it needs to be pointed out that, in tumours without EGFR mutation, docetaxel is superior to erlotinib in term of PFS with survival, results are pending (23) (TAILOR study).

The present data show the interest of erlotinib and, probably also gefitinib, in patients failing platinum-based chemotherapy when the EGFR mutational status is unknown. According to recent results, the place of TKI for wt tumours remains to be determined. As reported before, TKI in patients with NSCLC harbouring activating EGFR mutations have similar activity in first or second-line therapy.

In the clinical context, is there any different efficacy between gefitinib and erlotinib? Both drugs have never been compared in a randomized fashion. Based on a retrospective trial, activity of both agents appears similar in terms of response rate and survival in pretreated patients with metastatic or recurrent NSCLC (24). New EGFR TKIs with increased affinity for the EGFR kinase domain are currently developed. Icotinib did not demonstrate better activity than gefitinib in a phase III trial including previously treated NSCLC. Afatinib, an irreversible TKI, confirmed, its superiority as for gefitinib and erlotinib to chemotherapy in terms of RR and PFS in mutated tumors (25). Its comparison with gefitinib is expected.

A common problem in chemotherapy sensitive tumours is the development of resistant strains. Approximately 50 to 60% of acquired resistance is linked to an additional EGF-R mutation in which a methionine is substituted for threonine at position 790 on exon 20 (T790M). MET amplification, another mechanism of acquired resistance, is found in up to 20% of the cases. Different approaches are currently explored to overcome this point. Despite promising preclinical activity, results from prospective studies show limited activity of monotherapy with irreversible EGF-R TKI or combination therapy with erlotinib and heat shock protein 90 inhibitor or cetuximab (26-28). In patients with refractory NSCLC, sunitinib plus erlotinib did not improve OS compared with erlotinib alone, but the combination was associated with a statistically significantly longer PFS and greater ORR (29).

1) Monoclonal antibodies

Antibodies directed against the EGFR's ectodomain compete for ligand binding and induce recep-

tor endocytosis and finally receptor downregulation from the cell surface. Humanised (nimotuzumab, matuzumab), fully human (panitumumab) are currently tested but the most advanced compound is a chimeric monoclonal (murin humanised) antibody, IMC-C225 (Cetuximab, Erbitux®).

The phase III FLEX study compared (30) randomised patients with EGFR positive (>1 cell showing immunostaining for EGFR) IIIB (wet)-IV NSCLC to 6 cycles cisplatin (80 mg/m²) and Vinorelbine (25-30 mg/m²) with or without cetuximab (400 mg/m² then 250 mg/m² /week followed by maintenance until progression). A significant survival advantage was observed in the cetuximab arm. This effect was only noted when the tumour exhibited a frank EGFR immunostaining on a composite H score (intensity x % of positive cells; >200 on a maximum of 300).

FLEX and three others studies were included in a meta-analysis (31). The pooled HR for overall survival (HR, 0.87; 95%CI, 0.79-0.96; p=0.004) and overall response rate (RR, 1.19; 95%CI, 1.04-1.37; p=0.013) favoured the addition of cetuximab to chemotherapy. The analysis failed, however, to show a benefit of the combination on progression-free survival (HR, 0.91; 95%CI, 0.83-1.00; p=0.06) and one-year survival (RR, 1.10; 95%CI, 0.98-1.26; p=0.172).

2) Inhibition of angiogenesis

Angiogenesis is the formation of new blood vessels from the endothelium of the existing vasculature. After attaining a 1-2 mm size, further tumour growth and expansion requires the induction of new blood vessels. Although angiogenesis alone is not sufficient for the metastatic process, it increases the opportunity for malignant cells to enter the blood stream and thus to metastasise. Tumour angiogenesis is a complex multifactor process involving growth factor and extracellular matrix enzymes. A variety of proteins such as the vascular endothelial growth factor, the platelet-derived endothelial cell growth factor and the basic fibroblast growth factor, released by tumour cells, are recognised to be potent inducers of angiogenesis. Recent evidences suggest that tumour angiogenesis is associated with patient outcome in a number of malignancies including NSCLC.

Vascular Endothelial Growth Factor (VEGF) is the single most commonly upregulated angiogenic factor, rendering it a prime target for antivasculature therapy. One approach is to block the binding of all VEGF isoforms to the receptors inhibiting the biologic activities of VEGF using a recombinant humanised monoclonal antibody (Bevacizumab, Avastin®). Another option is to use small TKI molecules such as sorafenib or sunitinib.

Table 1. Randomized trial assessing EGFR-TKI (Gefitinib and Erlotinib) in NSCLC									
Study	N pts/line of treatment	Therapy	Phase	RR %	P	PFS	P	Survival	p
Gefitinib									
INTACT 1 (5)	1093/1 st line	Cisplatin -gemcitabine + placebo	III	47.2	NS	6.00m	0.76	10.9 m	0.45
		+ gefitinib 250 mg/d		51.2		5.8m		9.9 m	
		+ gefitinib 500 mg/d		50.3		5.5m		9.9 m	
INTACT 2 (4)	1025/1 st line	Carboplatin-paclitaxel+ placebo	III	28.7	NS	5 m	0.056	9.9 m	0.64
		+ gefitinib 250 mg/d		30.4		5.3 m		9.8 m	
		+ gefitinib 500 mg/d		30.0		4.6 m		8.7 m	
Mitsudomi (14)	172/1 st line	Gefitinib 250 mg/d	III			9.2	0.0001	NR	0.21
		Cisplatin docetaxel				6.3		30.9	
Maemondo (15)	228/1 st line	Gefitinib 250 mg/d	III	73.7	0.001	10.8	<0.001	30.5	0.31
		Chemotherapy		30.7		5.4		23.6	
IPASS (12)	1271 adenocarcinoma /1 st line	Gefitinib 250 mg/d	III	43.0	0.001		0.001	18.6	NS
		Carboplatin paclitaxel		32.2				17.3	
INTEREST (22)	1433/relapse	Gefitinib docetaxel	III	9.1		2.2m	0.47	7.6 m	NS
				7.6		2.7m		8 m	
ISEL (21)	1692 /relapse	Gefitinib 250 mg/d	III	8	<0.0001	3.0 m	0.0006	5.6 m	0.087
		Placebo		1		2.6 m		5.1 m	
Erlotinib									
TRIBUTE (6)	1079/1 st line	carboplatin/paclitaxel +placebo +erlotinib 150 mg/d	III	19.3	0.36	4.9	0.36	10.6	0.95
				21.5		5.1		10.8	
TALENT (7)	1172/1 st line	cisplatin/gemcitabine + placebo + erlotinib 150 mg/d	III	29.9	NS	24.6w	0.74	44.1w	0.49
				31.5		23.7w		43w	
BR21 (20)	731/relapse	placebo		1	<0.001	2.2	<0.001	4.7 m	0.001
		erlotinib 150 mg/d		9		1.8		6.7 m	

a. Bevacizumab

First line therapy

Two phase III trials testing bevacizumab have been conducted. In both, squamous cell carcinoma, those presenting with brain metastases or at high risk of bleeding were excluded. In the ECOG study, chemotherapy with carboplatin-paclitaxel (6 cycles) was administered with or without bevacizumab every three weeks until progression or unacceptable toxicity. The median PFS and survival were 6.2 and 12.3 months in the group assigned to chemotherapy plus bevacizumab, as compared with 4.5 and 10.3 months in the chemotherapy-alone group (hazard ratio for death, 0.79; $p=0.003$) (32). The results were not confirmed in the AVAIL study, the patients receiving 6 courses of gemcitabine-cisplatin +/- bevacizumab at 7.5 or 15 mg/kg until progression. A better response rate and an

improvement of the median progression free survival by 2 weeks with bevacizumab were observed but this did not translate into a survival benefit (33).

Salvage therapy

In patients with recurrent or refractory NSCLC, addition of bevacizumab to erlotinib does not improve survival (34).

b. Small TKI

The results with oral VEGF inhibitors are currently disappointing. In first line, sorafenib in combination with carboplatin-docetaxel showed no benefit but increased toxicity. Some promising results with salvage sunitinib observed in phase II needs further confirmation. Other drugs like vandetanib did not show improved survival in comparison to erlotinib in salvage

therapy (35) nor in combination with pemetrexed in comparison with pemetrexed alone (36).

3) Other mechanisms of action

EML4-ALK

An oncogenic genes fusion between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) is present in a small subgroup of non-small-cell lung cancers, representing 2 to 7% of non squamous tumours. Patients with ALK rearrangements tended to be younger, have little or no exposure to tobacco, and adenocarcinomas. In an early-phase clinical trial, crizotinib, an orally available small-molecule inhibitor of the ALK tyrosine kinase, showed an impressive response rate of 57% and a 33% stable disease rate (37). These results were confirmed in an expanded cohort (38). Crizotinib also showed a promising activity in ROS-1 tumours (39). Other compounds are under investigation.

Various

Many other genetic abnormalities are potential targets for targeted therapies. Mutations of BRAF, AKT, HER2, MEK, PIK3 or amplification of MET are detected in less than 2% of adenocarcinomas. Clinical studies with drugs targeting these mutations are ongoing. Downstream signaling pathways of RAS, ERK, MEK and mTOR are also explored. Finally, according to the new abnormalities found also in squamous cell carcinoma, drugs targeting FGFR1 amplification, DDR2 mutations and others are under investigation.

4) Toxicity

EGFR inhibitors, although generally well tolerated, have specific side effects. Skin toxicity is the most frequent one, presenting with acneiform rash (mostly in the head and neck region) and dry skin. Dermatological toxicity is often adequately treated with topical or oral antibiotics. Other frequent adverse events include diarrhea, fatigue and loss of appetite. A few patients (mostly Asian) are developing interstitial pneumopathy that can be life-threatening. Allergic reactions are frequent with cetuximab and pre-medication with anti-histamines and steroids is required. Crizotinib toxicity includes visual disorders, gastrointestinal side effects and elevated liver enzymes. These side effects are generally mild, not necessitating treatment interruption.

Antiangiogenic agents present with more serious toxicity which must be compared to the limited activity of these drugs. Hypertension, thromboembolic events

and hemorrhages are commonly reported and can be life-threatening.

CONCLUSION

Targeted therapies hold considerable promise in the treatment of patients with lung cancer. In selected patients, they may result in significant benefit with a quite low toxicity. However, their indiscriminate use is associated with higher costs and minimal clinical impact. Indeed, the efficacy of these drugs is dependent on the molecular profiles of the tumors. Well designed studies are needed to identify the subgroups of patients most likely to benefit from targeted treatments.

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