Review Article

Treatment of advanced non small cell lung cancer

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ABSTRACT Lung cancer is the major cause of cancer death in the world. Non Small Cell Lung Cancer (NSCLC) accounts approximately 80-85% of all lung cancer diagnosis; the majority of patients will be diagnosed with non operable, advanced-stage disease. Palliative chemotherapy and/or radiotherapy represent the standard of care of this disease. Platinum based doublets with third generation agents are considered the standard of first line advanced NSCLC treatment. However, data arising from the availability of pemetrexed suggest that histology could play a key role in decision making. Advances in understanding of the molecular pathogenesis of lung cancer have led to the identification of several specific targets such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) for therapeutic agents. Bevacizumab is the first recombinant humanized monoclonal antibody (mAb) binding VEGF to demonstrate clinical benefit and a rather survival prolongation in combination with chemotherapy in the treatment of non squamous chemo-naive advanced NSCLC patients. Two types of anti-EGFR targeting agents have reached advanced clinical development: mAbs and small molecule inhibitors of the EGFR tyrosine kinase enzymatic activity (TKIs). Among TKIs gefitinib has been tested in several phase II-III studies showing an improvement in survival and responses in first, second and third line treatment in selected patients with specific clinical and molecular characteristics. Furthermore, erlotinib has showed to significantly improve survival in an unselected population of patients following the failure of one or two chemotherapy regimens. This review will discuss the different therapeutic options for first and second line treatment in the clinical practice.

KEY WORDS non small cell lung cancer; pemetrexed; bevacizumab; erlotinib; gefitinib

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Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in the world. NSCLC is a heterogeneous aggregate of histologies, including squamous cell carcinoma, adenocarcinoma and large cell carcinoma, its represents approximately 80% to 85% of all lung cancers (1). While public awareness of this cancer and its associated early warning signs has improved along with the increasing use of screening techniques, the majority of patients will have advanced-stage non operable disease at the time of diagnosis.

The aim of treatment, in this setting of disease, is to slow down the progression of the disease, to relieve the patients from the lung cancer symptoms and, whenever possible, to increase the overall survival (OS). In first line treatment doublets containing platinum compounds represent the standard of care in advanced NSCLC, reporting a response rate (RR) racing from 20% to 35% with a median survival time (MST) of about 10 months (2). However, most patients receiving front-line chemotherapy experience disease progression. The availability of several new active drugs in second-line treatment suggests that this strategy can now be considered a standard of care for patients with a good performance status (PS) who progressed to first-line treatment. The chemotherapeutic agents docetaxel and pemetrexed and the biologic agent erlotinib are now available in clinical practice. The major progresses in the understanding cancer biology and mechanism of oncogenesis have allowed to identify several potential molecular targets for cancer treatment such as vascular endotelial growth factor (VEGF) and its receptors (VEGFRs) and epidermal growth factor receptor (EGFR).

Bevacizumab, an anti-VEGF recombinant humanized mAb, and the EGFR small molecules inhibitors such as gefitinib and erlotinib are now available in clinical practice in first or second-line treatment.

This review will discuss the current status of first and second

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line treatment in the management of advanced NSCLC patients.

First line treatment of advanced NSCLC

The role of chemotherapy in clinical practice

Since 1990s, it was demonstrated that for suitable patients (good PS), cisplatin-based chemotherapy is associated with a small survival advantage over best supportive care (BSC) in metastatic NSCLC. The available in the past decade of newer cytotoxic agents with activity in the management of NSCLC led to the development of a large number of clinical trials testing these agents either alone or in combination with platinium based chemotherapy. The results of four large multicenter randomized clinical trials evaluating these agents in combination with either cisplatin or carboplatin have been reported over the past few years and have yielded similar results (3-6). It is clear from these studies that no single regimen demonstrated a significant superiority over any other combination. In these studies median OS was approximately 8-10 months. However, in the last three years important advances have been achieved in the treatment of advanced NSCLC (7).

Histology of NSCLC has never been essential in the choice of first-line treatment; however, recent evidences arising from the availability of pemetrexed show that histology represents an important variable in decision making (8).

Pemetrexed is a novel multi-targeted antifolate chemotherapy agent; its primary mechanism of action is to inhibit at least three different enzymes in the folate pathway: thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT) (9).

In vitro studies indicated that tumour cell lines expressing high levels of TS or DHFR have reduced sensitivity to pemetrexed, suggesting that increased expression levels might correlate with reduced clinical efficacy (10).

A large non-inferiority phase III trial randomized chemotherapy-naive advanced NSCLC patients to receive either cisplatin plus gemcitabine or cisplatin at the same dose plus pemetrexed for a maximum of six cycles. OS, the primary end-point of this study, was 10.3 months in both arms (HR 0.94; 95% CI, 0.84 to 1.05) and survival rates at 1-year were 43.5% and 41.9% for cisplatin/pemetrexed and cisplatin/gemcitabine, respectively. Progression free survival (PFS) was also non-inferior (4.8 vs 5.1 months, respectively; HR 1.04) and RR was 30.6% in the cisplatin/pemetrexed arm compared to 28.2% in cisplatin/gemcitabine arm. For cisplatin/pemetrexed combination treatment, the rates of grade 3/4 neutropenia, anaemia, and thrombocytopenia (P<0.001); febrile neutropenia (P=0.002); and alopecia (P<0.001) were significantly lower, whereas grade 3/4 nausea (P=0.004) was more common(11).

A pre-planned analysis of this trial for histology subtype of NSCLC, reported that non-squamous patients had a longer MST on cisplatin/pemetrexed (11 months) than on cisplatin/gemcitabine (10.1 months; HR 0.84, P=0.011); adenocarcinoma 12.6 vs 10.9 months, respectively (HR 0.84, P=0.03); large-cell carcinoma: 10.4 vs 6.7 months, respectively (HR 0.67, P=0.03). Whereas squamous patients had a MST of 10.8 months on cisplatin/gemcitabin compared to 9.8 with cisplatin/gemcitabine (HR 1.23, P=0.05). The OS for patients with a generic diagnosis of NSCLC not otherwise specified (NOS), did not show a significant difference in survival between the two treatment arms. Similarly, non-squamous patients showed a trend that was not statistically significant for a longer PFS time on cisplatin/pemetrexed than on cisplatin/gemcitabine (5.26 and 4.96 months, respectively HR 0.95, P=0.349). Squamous patients had a shorter PFS time on cisplatin/ pemetrexed than on cisplatin/gemcitabine (4.4 and 5.5 months, respectively; HR 1.36, P=0.002). RR were higher in the cisplatin/pemetrexed arm compared to cisplatin/gemcitabine arm in patients with adenocarcinoma (28.9% vs 21.7%) or other NSCLC histotypes (28.3% vs 21.2%); a higher RR occurred in patients with squamous cell carcinoma (23.4% vs 31.4%) on cisplatin/gemcitabine. For patients with large cell carcinoma, RR was not statistically different between the two treatment arms (12). These results may be due to a higher expression of TS in squamous cell carcinoma and lower in adenocarcinomas, leading to lower sensitivity to pemetrexed in the squamous and higher in adenocarcinoma histotype.

Based on these data pemetrexed in combination with cisplatin has been granted as first-line treatment of patients with advanced NSCLC other than predominantly squamous cell histology.

Another smaller phase III trial comparing carboplatin plus pemetrexed or gemcitabine showed no significant difference in the primary end point (health-related quality of life) of this study. A higher rate of grade 3/4 hematologic toxicity was reported in patients who received gemcitabine/carboplatin compared to which treated with pemetrexed/carboplatin: leucopoenia (46% vs 23%, P<0.001), neutropenia (51% vs 40%, P=0.024), and thrombocytopenia (56% vs 24%, P<0.001). No difference in OS between the two treatment arms was reported (7.3 months in pemetrexed/carboplatin arm vs 7.0 months in gemcitabine/carboplatin arm; P=0.63). Multivariate analyses and interaction tests did not demonstrate any significant associations between histology and survival (13) (Table1).

The role of anti-angiogenic agents in clinical practice

Advances in understanding of the molecular pathogenesis of lung cancer have led to the identification of several specific targets for therapeutic agents. Angiogenesis is known to be essential for the development and progression of cancer. VEGF is a critical mediator in tumor angiogenesis for many

Table 1. Phase III randomized trials of gemcitabine versus pemetrexed within platin-based regimens, in first-line treatment of advanced nonsquamous NSCLC

Treatment	Pts	OS (m)	Author
CDDP plus GEM	1725	10.3 (global population) 10.9 (pts with adenocarcinomas)	Scagliotti, 2008 (12)
vs			
CDDP plus PEM		10.3 (global population) 12.6 (pts with adenocarcinomas)	
CBDCA plus GEM	436	7.0	Gronberg, 2009 (13)
vs			
CBDCA plus PEM		7.3	

Pts: patients; OS: overall survival; m: months; CDDP: cisplatin; GEM: gemcitabine; PEM: pemetrexed; CBDCA: carboplatin

solid malignancies, including NSCLC cancer. Inhibition of tumor-related angiogenesis has become an attractive target for anticancer therapy.

Bevacizumab

Bevacizumab is a humanized mAb directed against the VEGF; its consists of 93% human and 7% murine components and it recognizes all isoforms of VEGF ligands with Kd of 8 x10-10 M. Bevacizumab contains two identical light chains (214 amino acid residues) and two heavy chains (453 residues) with a total molecular weight of 149 kDa (14).

Two randomized phase III trials compared the combination of bevacizumab with chemotherapy versus chemotherapy alone in the treatment of advanced NSCLC.

The first multicenter phase III clinical trial (ECOG 4599) evaluated bevacizumab plus carboplatin and paclitaxel (BCP, pts = 434) versus carboplatin and paclitaxel alone (CP, pts = 444) in advanced chemo-naive non squamous NSCLC patients. OS was significantly longer in patients receiving BCP compared to those treated with chemotherapy alone (12.3 vs 10.3 months, respectively; HR 0.80, P=0.003); PFS was 6.2 and 4.5 months (HR 0.66, P<0.001) in the two treatment arms, with a corresponding RR of 35% and 15%, respectively (P<0.001) (15).

The addition of bevacizumab to chemotherapy resulted globally well tolerated, but more toxic then chemotherapy alone, the rates of clinically significant bleeding were 4.4% and 0.7% respectively (P<0.001).

A pre-planned subgroup analysis of this trial regarding the survival and safety outcomes based on histology has been recently published. For adenocarcinoma histology an increased OS has been reached for patients receiving BCP compared to patients treated with chemotherapy alone (14.2 months vs 10.3 HR 0.69). No unexpected toxicities have been observed among histology subtype (16).

The restriction of the patients population to non squamous histology, based on life-threatening or fatal haemoptysis occurring in 4 of 13 patients with squamous histology who received a BCP regimen in a phase II study, have determined in this trial a lower incidence of grade ≥3 pulmonary hemorrhage (17). Regarding the squamous histology, a retrospective analysis of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage reported only the baseline tumor cavitation as a potential risk factor with no influence by squamous histology and tumor central localization.

Recently, a phase II trial (BRIDGE) evaluated the safety of adding bevacizumab to carboplatin/paclitaxel chemotherapy in forty-seven untreated advanced squamous NSCLC patients. The incidence of grade ≥ 3 pulmonary haemorrhage in this study was 3.2% (1 pt) and no new safety signals were identified, however other clinical trials will performed to clarify this question (18).

Another large phase III trial (AVAIL) evaluated the combination of bevacizumab (15 mg/kg or 7.5 mg/kg every 3 weeks until disease progression) with gemcitabine /cisplatin versus the same chemotherapy regimen without bevacizumab in previously untreated, advanced non-squamous NSCLC patients. A significantly longer PFS, the primary study endpoint, was observed in patients randomized to receive bevacizumab therapy [6.1 months in the control arm, 6.7 (HR 0.75, P=0.002), and 6.5 months (HR 0.82, P= 0.03) in 7.5 mg/kg, and 15 mg/kg bevacizumab arms, respectively]; also the RR and response duration were significantly increased in both bevacizumab treatment arms (20%, 34%, and 30.4%, in the control, 7.5 mg/kg, and 15 mg/kg bevacizumab arms, respectively) (19). No difference in median OS was observed among all treatment groups (20). It is likely that the unprecedented high use of multiple second-line therapies in this trial is the main reason why the PFS benefit did not translate into an OS benefit. The ECOG 4599 and AVAIL trials represent the first evidence of an improvement in treatment outcomes of chemotherapy with targeted therapies in the first line treatment of advanced NSCLC (Table 2).

Bevacizumab is currently licensed for use in combination with

carboplatin plus paclitaxel for the first line therapy at dose of 15 mg/kg in patients with advanced NSCLC in United States, or in addition to platinum based chemotherapy in Europe at dose of 7.5 mg/kg or 15 mg/kg.

A meta-analysis of four randomized phase II-III study testing the addition of bevacizumab to different platinum-doublets as first line treatment of NSCLC, has been recently reported. This meta-analysis demonstrated an improvement in both OS (HR 0.89; P=0.03) and PFS (HR 0.72; P<0.001) in patients treated with bevacizumab plus chemotherapy. Patients with adenocarcinoma histlogy, recurrent or IIIb stage, non white race and body weight loss ≤ 5% had a significant higher OS compared to other corresponding group of patients (21).

The results of a multicenter, single-arm study (SAIL) have confirmed, in a real-world population, the safety and efficacy outcomes of bevacizumab treatment just reported in pivotal phase III trials (22).

Data emerging from several studies confirm the safety of bevacizumab-based therapy for the treatment of NSCLC patients with treated central brain metastases (CNS) (23,24).

However, further safety data have demonstrated that the risk of bleeding is similar in patients with untreated brain metastases receiving bevacizumab compared to those do not across various tumor types.

Based on these data, the EMEA that approved the drug use combined to any platin-based chemotherapy, removed the controindication concerning the use of bevacizumab in untreated CNS (25).

The role of EGFR inhibitors in clinical practice

Monoclonal antibodies: Cetuximab

Cetuximab is a chimeric human/murine IGg1 mAb that selectively bind to the extracellular domain of EGFR on the tumour cell, thereby inhibiting receptor-associated tyrosine kinase activation (26,27).

A large randomized phase III trial (FLEX), tested a platinum-based chemotherapy (cisplatin/vinorelbine) versus the same chemotherapy regimen plus cetuximab as first line treatment in EGFR-detectable advanced NSCLC patients.

The combination regimen has demonstrated a small but statistically significant benefit in survival over chemotherapy alone (11.3 vs 10.1 months, respectively; HR 0.871, P=0.0441) in all histology subgroups of NSCLC. An higher ORR was reported in patients receiving cetuximab (36% vs 29%, P=0.010), without a difference in PFS (median 4.8 months in both groups, HR 0.943). The grade 3 acne- like rash was the main cetuximab related adverse event (AE) and it occurred in 10% of patients enrolled in this trial.

This is the first study to demonstrate a survival benefit of an EGFR-targeted agent in combination with platinum-based chemotherapy in advanced first-line NSCLC irrespective of histology (28).

Another multicenter randomized phase III clinical study (BMS 099) compared the combination of cetuximab plus carboplatin/ taxanes versus chemotherapy alone in advanced NSCLC. The addition of cetuximab to chemotherapy did not significantly improve PFS (4.40 months in cetuximab/ chemotherapy arm vs 4.24 months with chemotherapy alone; HR 0.902, P=0.236). Median OS was 9.69 months in the combination arm versus 8.38 months in chemotherapy group (HR 0.890, P=0.169), however the survival benefit was similar to that observed in FLEX trial, but no statistically significant. An increase RR was reported in the combination arm compared to chemotherapy alone (25.7% and 17.2%, respectively P=0.007) (29) (Table 3).

A meta-analysis of individual patient data from four randomized phase II-III studies evaluated the effect of adding cetuximab to chemotherapy for the first-line treatment of advanced NSCLC. All efficacy results including OS, PFS and ORR were improved in cetuximab treated patients (HR 0.88 P=0.009; HR 0.90 P 0.045; P<0.001); and a favorable safety profile for chemotherapy plus cetuximab combination was also reported in this meta-analysis (30).

EMEA rejected the registration request for cetuximab combined to chemotherapy but a further final decision is now pending.

EGFR tyrosine kinase inhibitors: Gefitinib and Erlotinib

Gefitinib

Gefitinib is an orally available, reversible and selective EGFR-TKI, the first to have reached clinical trial testing.

The role of gefitinib as first line treatment in combination with chemotherapy has been evaluated in two large randomized phase III INTACT1 and INTACT2 trials (31,32). One thousand hundred ninety three patients in INTACT 1 and one thousand hundred thirty three in INTACT 2 study were randomized to receive gefitinib (250 mg or 500 mg daily) in combination with cytotoxic agents (cisplatin/gemcitabine) or (carboplatin/paclitaxel), respectively. No survival advantage and no difference in the secondary end points including RR and time to progression (TTP) was seen with the addition of gefitinib to chemotherapy, in either trial

The major challenge for an optimal use of EGFR targeting drugs is to define which patients are more likely to have a therapeutic advantage from the treatment. Clinical data suggest that TKIs are more active in certain NSCLC histotypes such as in adenocarcinomas and in bronchioloalveolar carcinomas, in women, in never smoker, in Asian ethnicity patients (33,34).

In 2004, three research groups have identified somatic gene mutations within the kinase domain of EGFR, related to the

Table 2. Phase III randomized trials of bevacizumab plus chemotherapy in first-line treatment of advanced nonsquamous NSCLC

Treatment	Pts	RR (%)	PFS (m)	OS (m)	Author
CBDCA / PTX plus BEV	878	35	6.2	12.3	Sandler, 2006 (15)
vs					
CBDCA/ PTX		15	4.5	10.3	
		(P<0.001)	(P=0.001)	(P=0.003)	
			HR=0.66	HR=0.79	
CDDP/GEM plus BEV	1043	34	6.7	13.6	Reck, 2009 (18)
vs					
CDDP /GEM		20	6.1	13.1	
			(P=0.002)	P=NS	
			HR=0.75	HR=0.94	

Pts: patients; RR: response rate; PFS: progression-free survival; OS: overall survival; m: months; NS: not significant; CBDCA: carboplatin; PTX: paclitaxel; BEV: bevacizumab; CDDP: cisplatin; GEM: gemcitabine

Table 3. Phase III randomized trials of cetuximab as first line treatment of advanced NSCLC

Treatment	Pts	RR (%)	PFS (m)	OS (m)	Author
CDDP/VNR plus Cetuximab	1125	36	4.8	11.3	Pirker, 2009 (26)
vs					
CDDP/VNR		29	4.8	10.1	
				(P=0.0441)	
DCA/TAXANES plus	676	25.7	4.40	9.69	Lynch,2010 (27)
Cetuximab					
vs		17.2	4.24	8.38	
CBDCA/TAXANES			(P=0.236)	(P=0.169)	

Pts: patients; RR: response rate; PFS: progression-free survival; OS: overall survival; m: months; CBDCA: carboplatin; CDDP: cisplatin; VNR: vinorelbine

response to EGFR TKIs (35-37). EGFR mutations were most frequently detected in a subpopulation of NSCLC patients with characteristics associated with a better treatment outcome: female sex, non smokers, Asian origin, adenocarcinoma histology. Approximately 90% of EGFR gene mutations affect small region of the gene within the exons (18 to 24) which code for the TK domain. The more common mutations are an in frame deletion in exon 19 around codons 746 to 750 (45% - 50% of all somatic EGFR mutations) and a missense mutation leading to leucine to arginine substitution at codon 858 (L858R) in exon 21 (35- 45% of all EGFR mutations) (38).

Several randomized phase III studies have compared gefitinib to platinum-based chemotherapy in advanced NSCLC patients.

In the IPASS trial (Iressa Pan-Asia Study), advanced NSCLC patients selected by clinical characteristics (never or light smokers, adenocarcinoma histology) were randomly assigned to receive gefitinib or carboplatin plus paclitaxel.

The 12-month rates of PFS were 24.9% with gefitinib and 6.7% with carboplatin-paclitaxel (HR 0.74, *P*<0.0001) (39); although OS did not differ between the two groups: 21.6 months for who began the study on gefitinib compared to 21.9 months of patients who had started on chemotherapy (*P*=1.00) (40).

In EGFR mutation positive patients (261 pts), PFS was significantly longer in patients receiving gefitinib compared to those treated with carboplatin-paclitaxel (HR 0.48; 95%; *P*<0.001); whereas in the subgroup of EGFR wild type (176 pts), PFS was significantly longer in patients receiving carboplatin-paclitaxel (HR for progression or death with gefitinib, 2.85; 95%; *P*<0.001).

Also the ORR was higher in patients with EGFR mutated tumors than in those without receiving gefitinib (71.2% and 1.1%, respectively) (39).

In the First-SIGNAL study, Korean advanced NSCLC patients (adenocarcinoma histology and never smokers) were randomized to gefitinib or standard chemotherapy (gemcitabine/cisplatin) as first line treatment. OS was similar in both groups, although PFS at 1 year was superior in the gefitinib compared to chemotherapy group (20.3% and 5.0% respectively) and also quality of life (QoL) is improved in gefitinib group.

Moreover a subgroup analysis showed an OS of 30.6 months

in EGFR mutations positive patients and 18.4 months in those without mutations (HR 0.845; *P*=0.643) treated with gefitinib and a PFS of 8.4 and 2.1 months, respectively (HR 0.394; *P*= 0.0006); the ORR was also dramatically better in this subgroup of patients (84.6% and 25.9%; respectively) (41).

In the WJTOG3405 trial, chemotherapy-naive advanced NSCLC patients harbouring EGFR mutations were randomly assigned to receive gefitinib or chemotherapy (cisplatin/docetaxel). In gefitinib arm a longer PFS was reported compared to chemotherapy group (9.2 and 6.3 months; HR 0.489, log-rank *P*<0.0001, respectively); as well the RR was higher in patients tretated with gefitinib (62.1% and 32.2%, respectively) (42).

In a more recent trial (NEJ002) gefitinib was compared to carboplatin/paclitaxel in EGFR mutated advanced NSCLC patients. After a planned interim analysis this trial has been interrupted since a significantly longer median PFS (10.8 vs 5.4 months; HR, 0.30; *P*<0.001), as well as a higher RR (73.7% vs 30.7%, P<0.001) was reported in patients treated with gefitinib. However the median OS was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group (*P*=0.31) (43) (Table 4).

These two phase III trials performed in EGFR mutated patients confirm once more gefitinib to be superior to chemotherapy in terms of PFS and RR suggesting that the EGFR gene mutational status play an important role in the treatment choice of advanced NSCLC.

Finally, based on these results the EMEA approved gefitinib for the treatment of advanced NSCLC patients harbouring EGFR mutations even in first-line setting.

Erlotinib

Erlotinib is an oral low molecular weight quinazoline-based agent which selectively and reversibly inhibits the kinase activity of EGFR (44).

As observed for gefitinib, the combination of erlotinib with platinum based polichemotherapy (carboplatin/paclitaxel and cisplatin/gemcitabine in TRIBUTE and TALENT phase III trials, respectively) in advanced NSCLC chemo-naïve patients, demonstrated to confer no survival advantage over chemotherapy alone (45,46).

Several phase II trials tested erlotinib as monotherapy in unselected chemo-naive advanced NSCLC patients showing interesting results (47-49).

A large randomized phase III trial (TORCH) compared erlotinib followed by chemotherapy (cisplatin/gemcitabine) versus the same chemotherapy regimen followed by erlotinib in advanced NSCLC unselected patients (standard Arm). This trial was early stopped based on planned interim analysis showing an HR of 1.40 for death in experimental arm *P*=0.002 and a median OS of 7.7 vs 10.8 months in the standard arm (50).

In another phase III trial chemo-naïve advanced NSCLC patients (ECOG PS 2/3 or PS 0/1 unfit for platinum chemotherapy) were randomized to erlotinib plus BSC or placebo plus BSC. Erlotinib did not improve OS (HR 0.98; *P*=0.77). Pre-specified subgroup analyses showed significant longer OS and PFS for females (HR 0.75; *P* = 0.04 and HR 0.64, *P*< 0.001; respectively) and a clear effect on PFS was also seen for adenocarcinoma histology (HR 0.74; *P*= 0.03) (51).

The important role of EGFR activating mutations suggests the relevance of patient selection to identify which could gain interesting clinical benefit by erlotinib as front-line therapy.

In a recent phase III trial (OPTIMAL) EGFR mutated Asian NSCLC patients were randomly assigned to receive erlotinib or "doublet" combination chemotherapy of gemcitabine and carboplatin. The PFS in erlotinib arm was 13.1 compared to 4.6 months in chemotherapy arm and a higher RR was also achieved in erlotinib arm (83% vs 36% respectively). Subgroup analysis showed a consistent benefit with erlotinib regardless of histology, smoking history, age, sex, and disease stage.

OPTIMAL is the first prospective trial to confirm the role of erlotinib in advanced NSCLC patients with EGFR activating mutations (52) (Table 4).

An important prospective phase III ongoing trial (EURTAC) will evaluate the efficacy of erlotinib compared with chemotherapy in advanced caucasian NSCLC patients harbouring EGFR gene mutations. The final results of this trial are expected next year.

Second-line treatment in advanced non small cell lung cancer

After or during first-line treatment several NSCLC patients have experience of disease progression with a limited life expectancy. Numerous variables such as disease-related symptoms, residual toxicity of previous chemotherapy, and co morbid diseases, could compromised the QoL. Life expectancy of these patients is largely dependent on their PS at the start of second-line treatment.

In recent years, the efficacy of several drugs in the second-line setting has been demonstrated and second-line treatment can now be considered a standard of care (53). Two chemotherapeutic agents, docetaxel and pemetrexed, and erlotinib are currently approved for the second line treatment of unselected NSCLC patients, while gefitinib is approved for clinical use only in patients with EGFR mutated tumors.

Docetaxel

In a phase III trial (TAX317), docetaxel 100 mg/m^2 was compared to BSC. The protocol was amended and the dose was reduced to 75 mg/m^2 after the evidence of a significantly higher toxic death rate in the chemotherapy arm.

A longer TTP was observed for docetaxel compared to

Table 4. Phase III randomized trials of gefitinib or erlotinib as first line treatment of advanced NSCLC

Treatment	Patients	RR (%)	PFS (m)	OS (m)	Author
PTX plus CBDCA	1217	32.2	6.7%	21.6	Mok, 2009 (36)
vs					
Gefitinib		43.0	24.9%* (P<0.001)	21.9 (P=1.00)	Yang, 2010 (37)
CDDP plus GEM	313	45.3	5.0 %	NR	Lee, 2009 (38)
vs					
Gefitinib		53.5	20.3%*		
CDDP plus TXT	177	32.2	6.3	NR	Mitsudomi, 2010 (39)
vs					
Gefitinib		62.1	9.2 (P<0.0001)		
CBDCA plus PTX	228	30.7	5.4	23.6	Maemondo, 2010 (40)
vs					
Gefitinib		73.7	10.8 (P<0.001)	30.5 (P=0.31)	
CDDP plus GEM →Erlotinib	760	NR	NR	10.8	Gridelli, 2010 (47)
vs					
Erlotinib → CDDP plus GEM				7.7 (P=0.002)	
Erlotinib plus BSC	670	NR	HR 0.86 [95% CI 0.74-1.01; P=0.07]	HR 0.98 [95% CI 0.82-1.15; P=0.77]	Lee, 2010 (48)
vs					
Placebo plus BSC					
CBDCA plus GEM	154	36	4.6	NR	Zhou, 2010 (49)
vs					
Erlotinib		83 (P=0.0000)	13.1 (P<0.0001)		

*1 year rates. Pts: patient=s; RR: response rate; PFS: progression-free survival; OS: overall survival; m: months; NR: not reported; CBDCA: carboplatin; PTX: paclitaxel; CDDP: cisplatin; GEM: gemcitabine; TXT: docetaxel; BSC: best supportive care; HR: hazad ratio; CI: confidence interval

BSC (10.6 vs 6.7 weeks, respectively; $P<0.001$); also OS was significantly longer for patients receiving docetaxel (7.0 vs 4.6 months; $P=0.047$). Febrile neutropenia was the most common toxicity related to docetaxel treatment observed (11 pts in docetaxel 100 mg/m^2, three of whom died, and 1 patient in docetaxel 75 mg/m^2) (54).

In another phase III study (TAX 320), patients were randomly assigned to receive docetaxel at dose of 100 mg/m^2 or 75 mg/m^2 every 3 weeks, or vinorelbine or ifosfamide at the investigator's discretion.

Patients in docetaxel arm achieved a longer TTP ($P=0.046$) and PFS at 26 weeks ($P=0.005$). Although no significant difference in OS was reported between the three treatment arms, however the 1-year survival rate was significantly higher with docetaxel 75 mg/m^2 compared to the control treatment (32% vs 19%; $P=0.025$).

A greater ORR has been reported in both docetaxel arms (10.8% for docetaxel at dose of 100 mg/m^2 and 6.7% at 75 mg/m^2), compared to vinorelbine or ifosfamide (0.8% $P=0.001$ and $P=0.036$, respectively). Patients received docetaxel had more neutropenia and febrile neutropenia compared to control arm, but the lower dose of docetaxel was generally well tolerated (55).

Based on the results of these two phase III trials docetaxel was the first drug to be approved for second-line treatment of advanced NSCLC.

Considering the toxicities related to standard 3-week schedule of docetaxel including fatigue, myelosuppression and pain, several randomized clinical studies have been conducted to compare the standard schedule with the weekly schedule. The results of these trials suggest a better toxicity profile for weekly regimen but contrasting results regarding the OS (56-60).

A meta-analysis based on individual data from patients enrolled in five randomized trials has compared the efficacy of the two different schedules of docetaxel for second-line treatment of NSCLC. No survival difference between the two schedules, with a HR estimate of only 1.09, has been observed.

This analysis confirms a significantly different toxicity profile between the two schedules of docetaxel as febrile neutropenia that is significantly lower with weekly schedule.

In conclusion, weekly docetaxel may be a valid alternative to standard 3-weekly schedule for all NSCLC patients who are candidates for a second-line chemotherapy (61).

Pemetrexed

In a phase III trial advanced NSCLC patients after failure of one prior chemotherapy regimen, were randomly assigned to receive pemetrexed or docetaxel. The ORR was 9.1% and 8.8%, the MST 8.3 vs 7.9 months (P = not significant) for pemetrexed and docetaxel, respectively. A median PFS of 2.9 months and the 1-year survival rate of 29.7% were reported in each arm. Pemetrexed produced similar results and was better tollerated than docetaxel, in-fact an higher incidence of grade 3-4 neutropenia, neutropenic fever and neuropathy was reported in docetaxel arm (62).

A retrospective analysis of this trial showed no significant difference in outcome or toxicity between elderly and younger patients (63). Elderly patients receiving pemetrexed or docetaxel had a MST of 9.5 and 7.7 months compared to 7.8 and 8.0 months for younger patients treated with pemetrexed or docetaxel respectively. Elderly patients treated with pemetrexed had a longer TTP and OS than their counterpart patients treated with docetaxel (not statistically significant). Pemetrexed demonstrates a more favorable toxicity profile than docetaxel: febrile neutropenia was less frequent in elderly patients treated with pemetrexed (2.5%) compared to those receiving docetaxel (19%; P=0.025).

A different activity of pemetrexed in different histotypes of NSCLC has been also confirmed in the second-line treatment by a retrospective analysis of this trial. A longer OS was observed in non-squamous patients receiving pemetrexed than docetaxel (9.3 vs 8.0 months; HR 0.78; P=0.047), conversely squamous patients had a shorter OS with pemetrexed treatment compared to docetaxel (6.2 vs 7.4 months; HR 1.56; P= 0.018). Non-squamous patients had a little longer PFS with pemetrexed than docetaxel (3.1 vs 3.0 months; HR 0.82; P=0.076), while squamous patients achieved a little shorter PFS on pemetrexed than docetaxel (2.3 vs 2.7 months, respectively; HR 1.40; P=0.046). Differences in RR according to histology were also observed; in fact a higher RR was reported in adenocarcinoma or large cell carcinoma patients receiving pemetrexed compared to those treated with docetaxel; whereas in patients with squamous or other NSCLC histology RR favoured docetaxel (64).

A phase III study compared high dose (900 mg/m2) to standard dose of pemetrexed in advanced NSCLC patients after failure of one platinum based chemotherapy regimen. No statistical difference was reported between two treatment groups for MST (6.7 vs 6.9 months, HR 1.0132), PFS (2.6 vs 2.8 months, HR 0.9681) or best ORR (7.1% vs 4.3%; P=0.16); however the incidence of toxicities were higher in experimental arm (65).

Erlotinib

In a phase III, placebo-controlled trial (BR21) erlotinib was compared to BSC in pre-treated advanced NSCLC patients who have received one or two regimens of combination chemotherapy and not be eligible for further chemotherapy. The RR was 8.9% in the erlotinib arm and less than 1% in the placebo group (P<0.001); a PFS of 2.2 and 1.8 months was reported, respectively (P<0.001; HR 0.70). A significant survival advantage of 2 months was observed in all patients subgroup treated with erlotinib compared to placebo (P<0.001; HR 0.7) (66).

An analysis of this trial showed that smoking status may be the most important predictor of a survival benefit with erlotinib treatment in fact never smokers treated with erlotinib had a significantly higher survival rate than patients receiving placebo (HR 0.4; P=0.01) (67).

A QoL analysis has demonstrated a significant benefit of erlotinib in improving not only survival but also time to deterioration for all three major symptoms related to the disease (cough, dyspnoea and pain) (68). Based on these results, erlotinib has been approved by the FDA and EMEA in October 2005 for the treatment of chemotherapy-resistant advanced NSCLC patients and is actually approved worldwide for second and third-line treatment of unselected advanced NSCLC patients.

The large, global, open-labeled, phase IV trial TRUST study included more than 6,500 patients evaluated safety and efficacy of erlotinib in patients with advanced stage IIIB/IV NSCLC who had previously failed on or were considered unsuitable to receive standard chemotherapy or radiotherapy and were ineligible for other erlotinib trials. In patients with advanced NSCLC, the PFS and OS in this study were 3.25 months and 7.9 months, respectively, and the disease control rate was 69% .Results from the TRUST study suggest that erlotinib can benefit a wide range of patients, including those who have previously been thought unlikely to benefit from this treatment (69).

Gefitinib

A large multicenter, randomized phase III trial (INTEREST), has compared gefitinib versus docetaxel in previuosly treated advanced NSCLC patients.

The results overall were very similar for the two treatments: MST for docetaxel-treated patients was 8.0 months compared to 7.6 months for patients receiving gefitinib (HR 1.020); 1-year survival rate was 34% and 32%, respectively. The RR was slightly higher with gefitinib, 9.1% vs 7.6%.

The superiority of gefitinib in patients with high EGFR-gene-

copy number (co-primary endpoint) was not met (72 vs 71 events; HR 1.09, *P*=0.62; MST 8.4 vs 7.5 months).

In the gefitinib group, the most common AE were rash or acne and diarrhoea whereas in the, neutropenia, asthenic disorders and alopecia were most frequently reported in docetaxel group (70).

Molecular analysis of biomarkers including EGFR copy number by fluorescent in situ hybridization (FISH), EGFR protein expression by immunohistochemistry (IHC), EGFR and KRAS mutations showed that survival was similar for gefitinib and docetaxel, with no statistically significant difference between treatments and no significant treatment by biomarker status interaction tests. However among EGFR mutated patients, PFS advantage in favour of gefitinib was reported (PFS; HR 0.16; *P*=0.001) and also a higher ORR was also observed (42.1% and 21.1%, respectively; *P*=0.04) (71).

In a phase III trial (V-15-32), pre-treated Japanese advanced NSCLC patients were randomized to receive gefitinib or docetaxel. Non-inferiority in OS was not achieved (HR 1.12) according to predefined criteria (upper CI limit for HR <1.25); however, no significant difference in OS (*P*= 0.330) or PFS (*P*=0.335) was evident between treatments. Gefitinib significantly improved RR, TTP and QoL compared to docetaxel. However, in this study cross-over of treatments was allowed, which would have possibly affected the survival results (72).

In a randomized phase III trial (ISTANA) has been compared gefitinib to docetaxel in pretreated Asian NSCLC patients. This study showed a longer PSF (HR 0.73), and an improvement in RR (28.1% vs 7.6%, *P*=0.0007) in favour to gefitinib (73).

In both trials, gefitinib provided RR around 25% and median PFS around 2 to 3 months representing in unselected East Asian patients the general treatment outcomes.

Gefitinib use is not actually approved by regulatory agencies in the second line treatment of unselected NSCLC patients.

Conclusion

In the last few years, relevant advances have been reached in advanced NSCLC treatment. Platinum-based chemotherapy is the standard of treatment for the majority of patients, however new chemotherapy drugs and targeted agents have expanded treatment options for this disease. Recent evidences suggest that histology represents an important variable in decision making. In fact, in first line treatment of non-squamous NSCLC patients, bevacizumab and pemetrexed have improved outcomes and modified treatment algorithms, while fewer therapeutic options are actually available for squamous histology patients which could be treated with chemotherapy containing platinum plus a third generation cytotoxic agent.

The identification of several factors, including both the genetic profile of the patients and the biological characteristics of the disease could guide the clinician's choice.

Considering the excellent benefit and better safety profile of gefitinib in patients with tumours harboring EGFR-mutations, it could represents the standard in first- line treatment for this subgroup of patients while erlotinib is waiting for the regulatory agencies approval.

Several agents are actually approved for the second line treatment, the choice of second line treatment is based on histological and biological characteristics of the tumor, PS of patients and on the drugs already used in first line.

In addition, novel cytotoxic agents are in clinical development including new platinum analogs such as picoplatin (a cisplatin analog), ABT-751 (a sulfonamide) and tubulin binding agents (TBAs) such as the epothilones. New targeted agents and their combinations with chemotherapy agents are also being explored in clinical research in hopes to improve treatment options for advanced NSCLC patients. Future challenges involve identifying predictors of response and efficacy for targeted therapies and selecting the optimal therapy for maximum survival benefit in

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