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REVIEW

Review of the treatment of metastatic non small cell lung carcinoma: A practical approach

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Abstract

In recent years, as we have a better knowledge and understanding of the biology of non small cell lung carcinoma (NSCLC), which leads us to targeting biomarkers driving the NSCLC carcinogenesis and metastatic potential, we now have an increased number of options to offer our patients with NSCLC. We also realize the importance of distinguishing squamous and non squamous histology to guide our treatment decisions of NSCLC. The palliative care concomitant with therapies from the very start of the treatment also showed an impact on survival. This review examines the treatment options in all lines of therapy for metastatic NSCLC that have been approved in Canada, the United States, or Europe.

Key words: Metastatic; Non small cell lung carcinoma; 1st Line; 2nd Line; 3rd Line; Treatment

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INTRODUCTION

Lung cancer remains one of the most common cancers worldwide and a leading cause of mortality, with an estimated 1.6 million new cases and nearly 1.4 million deaths annually. The majority of patients with non small cell lung carcinoma (NSCLC) present with advanced stage disease at diagnosis. A large number of patients who are diagnosed at an early stage will eventually experience disease relapse and will also need treatment for a metastatic disease. The 5-year survival rate of lung cancer patients remains only about 15%. Furthermore, advanced lung cancer causes debilitating symptoms which can seriously affect the quality of life (QOL) and survival.

Historically, the treatment of NSCLC has involved a finite number of cycles of first-line chemotherapy, the most commonly-used regimens being platinum doublets[1] for patients with a good performance status (PS) and no significant comorbidities, after which patients with tumour response or stable disease were observed for evidence of disease progression; at this point, suitable patients would start second-line therapy. We learned that the introduction of a third chemotherapeutic agent only increased toxicity, but not efficacy. We also realized that only about 50%-60% of patients go on to receive second-line therapy and of those, only 50%-60% will receive third-line therapy. It is therefore important to ensure that patients receive the best therapeutic option in each line of therapy[2].

In recent years, two new concepts have been introduced in the treatment of metastatic NSCLC: maintenance therapy and targeted biologic agents. Maintenance therapy after first-line therapy can be with either chemo-

therapeutic or biologic agents, it may include drugs given in the induction regimen, or different agents (i.e. "early" second-line treatment) with the aim of preventing progression and prolonging progression-free survival (PFS). Targeted agents, when compared with chemotherapeutic agents in this setting, show fewer toxicities, especially cumulative toxicities such as myelosuppression; thus the possibility of a longer duration of therapy[3].

Two main groups of targeted agents for NSCLC, which are presently approved in the United States, Canada, and Europe, based on the results of clinical trials, including their efficacy and safety profiles, are the inhibitors of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF). Erlotinib or gefinitib and bevacizumab are the respective representatives of these groups. Another EGFR inhibitor, cetuximab, is not currently approved in Canada and the United States. Gefitinib was granted marketing authorization for the treatment of EGFR mutation-positive metastatic NSCLC.

The options and lines of treatments in metastatic NSCLC are increasing. The understanding of the development of resistance to different therapeutic agents will help us to decide on the sequence of therapies i.e. the choices for first, second, third, and further lines of treatment. Our decisions will not only depend on age, gender, comorbidities, smoking history, racial origin, and PS of patients, but also on the tumour characteristics and the toxicity profile of the therapies.

The goal of the treatments of advanced NSCLC is only palliative for now, thus QOL remains a very important factor. Early control of symptoms such as nausea, diarrhoea, constipation, pain, or prevention of cytopaenias and bone metastases enables patients to maintain good PS and QOL, enabling them to receive now available numerous lines of treatments. We now better understand various prognostic and predictive factors which can guide our decisions regarding the different treatment options and help us to deliver a personalized, individualized treatment for our NSCLC patients, leading to increased treatment efficacy, decreased toxicity and improved QOL.

FIRST-LINE TREATMENT OF METASTATIC NSCLC

Chemotherapy in first-line

The third-generation chemotherapy agents such as paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, and pemetrexed in platinum-based doublets are more effective in terms of response rates and survival and are better tolerated than the older platinum-based combinations[4,5]. The overall benefit obtained by modifying chemotherapy regimens has been small and has yielded no tangible improvement in overall survival (OS)[6]. Median OS reached with chemotherapy plateaus at 8-10 mo, even with pemetrexed, as demonstrated in per protocol population in a phase Ⅲ trial[7] comparing first-line cisplatin-pemetrexed to cisplatin-gemcitabine, showed a median OS of 10.3 mo for each treatment arm.

In a pre-specified analysis, the median OS was significantly longer for cisplatin-pemetrexed than for cisplatin-gemcitabine in patients with adenocarcinoma histology [n = 847, 12.6 mo *vs* 10.9 mo, hazard ratio (HR) = 0.84, P = 0.03] and large-cell carcinoma histology (n = 153, 10.4 mo *vs* 6.7 mo, HR = 0.67, P = 0.03). The median survival of patients with squamous histology assigned to cisplatin-pemetrexed (n = 244) was only 9.4 mo; and was 10.8 mo on cisplatin-gemcitabine (n = 229, HR = 1.23, P = 0.05). For patients with NSCLC without further subtype classification (n = 252), no significant differences were observed between the two arms[7]. Thus, cisplatin-pemetrexed should not be given for squamous tumours. Carboplatin-pemetrexed demonstrated efficacy similar to that of carboplatin-gemcitabine in first-line treatment of metastatic NSCLC[8]. No comparison is yet available of the platinum-taxane regimens with the platinum-pemetrexed regimens. Carboplatin is favoured in certain centres and countries, especially in the more frail patients with different comorbidities, due to less toxicity.

Targeted therapies in first-line

The first targeted agent which when added to a platinum doublet in first-line metastatic NSCLC resulted in an improved efficacy, was the anti-VEGF monoclonal antibody, bevacizumab. VEGF has multiple roles in tumour angiogenesis. It has been shown to promote survival[9] and to increase permeability of existing tumour vasculature[10], while stimulating the growth of new tumour vessels[9]. In addition, VEGF is known to have a direct effect on tumour cells, including survival, migration, and invasion[10]. Two early effects of anti-VEGF therapy include regression of existing tumour microvasculature, and normalization of the remaining microvasculature, helping to better deliver chemotherapy to the tumour[11]. A third effect is the continued inhibition of the formation of new tumour vasculature[12].

Bevacizumab was tried in a phase Ⅱ trial (Figure 1), where it was added to carboplatin/paclitaxel. It significantly improved response rate and PFS in patients with advanced NSCLC[13].

The ECOG 4599 (Eastern Cooperative Oncology Group) phase Ⅲ trial demonstrated significant improvement in median OS (12.3 mo *vs* 10.3 mo, HR = 0.79, P = 0.003), median PFS (6.2 mo *vs* 4.5 mo, HR = 0.66, P < 0.001), and response rates (35% *vs* 15%, P < 0.001) for bevacizumab in combination with carboplatin-paclitaxel as compared with chemotherapy alone[14]. Bevacizumab is the first agent combined with chemotherapy to improve survival beyond 1 year for patients with non-squamous pathology of NSCLC. In the same trial in patients with adenocarcinoma, median OS was 14.2 mo *vs* 10.3 mo for control.

The AVAIL (AVASTIN in lung) trial was the second, randomized phase Ⅲ trial with cisplatin-gemcitabine and bevacizumab 7.5 mg/kg or 15 mg/kg *vs* cisplatin-gemcitabine only, in a three-arm study design. This study was conducted 4-5 years later than the ECOG study,

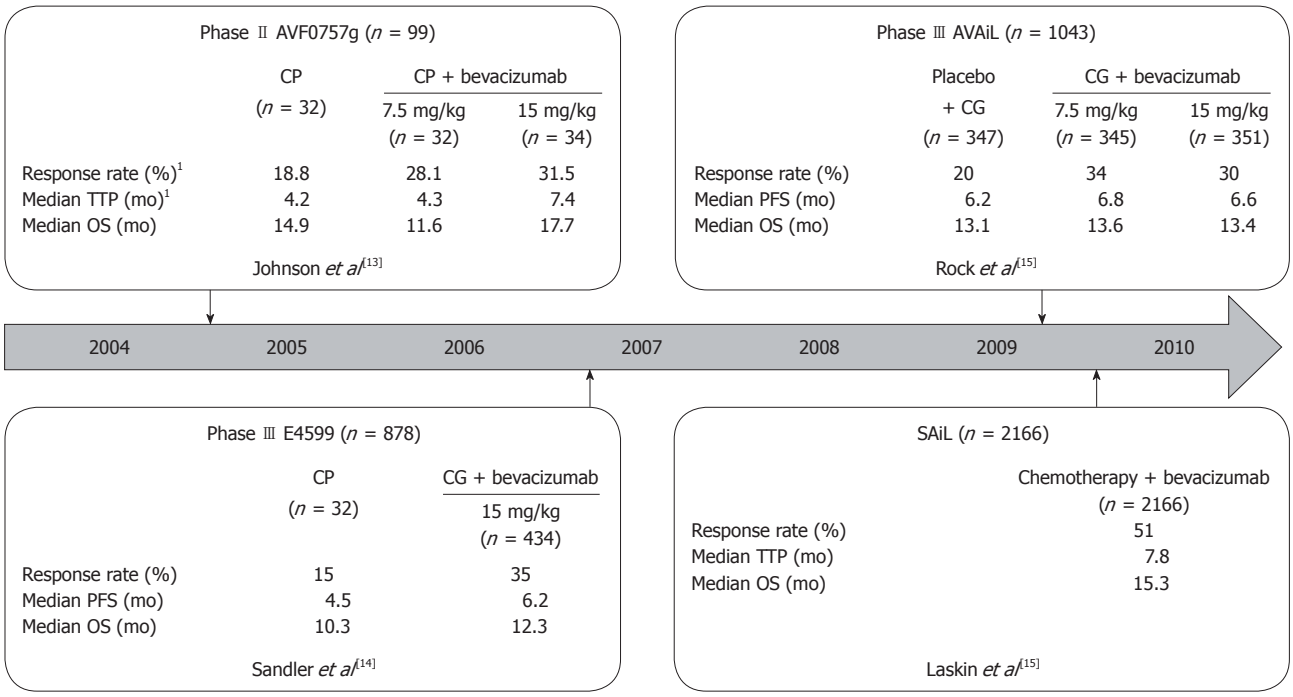

Figure 1 First-line bevacizumab data in non small cell lung carcinoma. CP: Carboplatin, paclitaxel; CG: Cisplatin, gemcitabine. [1]Investigator assessment.

when more lines of treatments were available and they could confound OS, and crossover to bevacizumab was possible, thus median PFS was a primary endpoint. PFS was significantly prolonged with bevacizumab 7.5 mg/kg plus chemotherapy compared with chemotherapy alone (6.7 mo *vs* 6.1 mo; HR = 0.75, $P = 0.003$) and an objective response rate of 34.1% compared to 20.1% for chemotherapy alone ($P < 0.0001$). PFS was also significantly improved in patients receiving bevacizumab 15 mg/kg plus chemotherapy as compared with placebo (6.5 mo *vs* 6.1 mo; HR = 0.82, $P = 0.03$).

The SAIL (Safety of Avastin in Lung) trial examined the safety of bevacizumab in a broad patient population[15,16]. More than 2000 patients demonstrated a clinical benefit with bevacizumab, not only with different cisplatin, but also carboplatin doublets - regimens according to the investigators' choice. In this trial, median PFS was 7.8 mo and median OS was 15.3 mo[15].

A 2000 patient registry trial in the United States ARIES, (Avastin Registry: Investigation of Effectiveness and Safety), showed similar results as the SAIL trial even though 647 patients were elderly > 70 years old. Some had hypertension, central tumour location, central nervous system (CNS) metastases, or receiving anticoagulation therapy. Median PFS was over 6 mo, and median OS was 13.3 mo[17]. A meta-analysis of more than 13000 bevacizumab-treated patients provided reassurance that the risk of CNS bleeding in patients with brain metastases is not increased[18].

In contrast, phase Ⅲ trials with cetuximab plus taxane-carboplatin (BMS - 099) and cetuximab plus cisplatin-vinorelbine in the FLEX (First line Erbitux) trial, failed to demonstrate a PFS benefit in patients with NSCLC (4.4 mo *vs* 4.2 mo and 4.8 mo, respectively)[19,20]. A marginal OS benefit was observed in FLEX (11.3 mo *vs* 10 mo), which raises the question of the benefit of subsequent post-induction therapies.

A large, phase Ⅲ trial ESCAPE, (Evaluation of Sorafenib, Carboplatin And Paclitaxel Efficacy in NSCLC) of sorafenib, a multikinase inhibitor in combination with carboplatin-paclitaxel, showed no benefit in patients with NSCLC. Moreover, the addition of sorafenib had a detrimental effect in patients with squamous cell histology. The trial was stopped prematurely and did not meet its primary OS endpoint[21].

The NCIC, (National Cancer Institute of Canada) BR.24 phase Ⅱ/Ⅲ study of cediranib in first-line NSCLC was also discontinued because of unacceptable toxicity. A follow-up, randomized phase Ⅲ trial (NCIC BR.29) is currently ongoing, testing cediranib at the lower dose of only 20 mg orally daily with carboplatin-paclitaxel compared to carboplatin-paclitaxel alone in patients with metastatic NSCLC. Many other randomized trials of targeted therapies combined with chemotherapy have failed to demonstrate clinical benefit.

Evidence-based medicine: a practical approach in first-line

A number of factors will affect the choice of first-line therapy in metastatic NSCLC, including available clinical data, patient characteristics (age, smoking history, histology, racial origin, tumour mutation status, patient preference, and physician's experience with certain agents. Although pemetrexed has demonstrated an OS benefit in patients with non-squamous NSCLC, that benefit was restricted to the sub-analysis of a subgroup of patients who

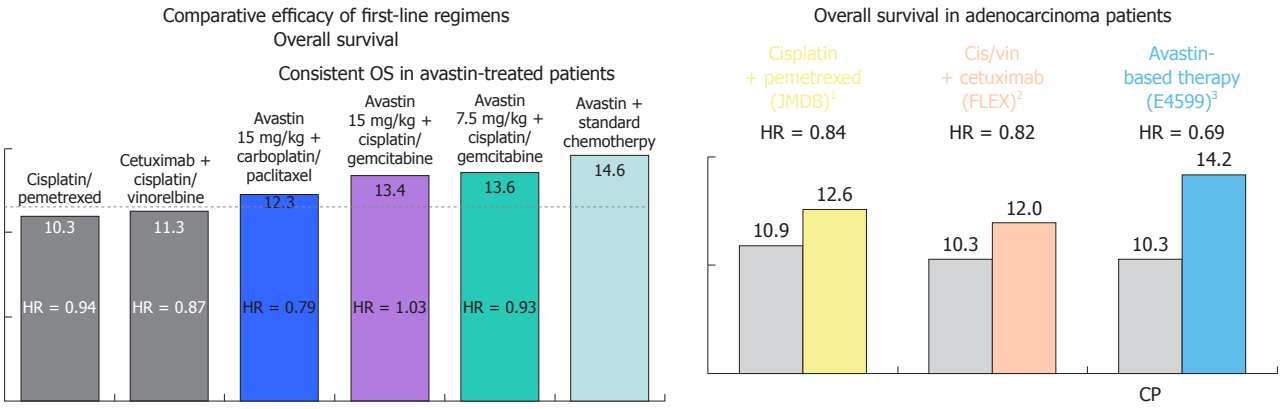

Figure 2 Comparison of overall survival with the most frequently given regimens in first-line treatment of metastatic non small cell lung carcinoma. [1]Scagliotti *et al*[7]; [2]Pirker *et al*[20]; [3]Sandler *et al*[14]. HR: Hazard ratio; OS: Overall survival.

received cisplatin. No comparison of platinum-taxanes with platinum-pemetrexed is available. Thus, patients not eligible for bevacizumab should receive platinum-containing doublet chemotherapy, of which cisplatin-pemetrexed is the most promising for non-squamous histology. Results from phase Ⅲ trials will help to determine the role of pemetrexed-platinum with bevacizumab in the first-line setting. A summary of OS with the most frequently used regimens in first-line treatment of NSCLC is shown in Figure 2.

The evidence suggests that EGFR tyrosine kinase inhibitors (TKIs) are particularly effective agents in patients with EGFR mutation-positive tumours. A phase Ⅲ trial, open-label study (the IRESSA Pan-Asia Study - IPASS)[22] examined the efficacy of gefitinib in first-line as compared with carboplatin-paclitaxel in clinically selected patients with NSCLC. The results revealed significantly longer PFS, increased objective response rates ($P < 0.0001$), and improved QOL among EGFR mutation-positive patients who received gefitinib than among those who received carboplatin-paclitaxel, but median OS was not statistically different. The difference in the rates of objective response with gefitinib was remarkable at 71.2% and 1.1% for EGFR mutation-positive and negative patients, respectively, median PFS was 9.5 mo on gefitinib compared to 6.3 mo on chemotherapy (HR = 0.48, $P < 0.0001$), and median OS was 21.6 mo *vs* 21.9 mo, respectively, in mutation-positive patients (HR = 1.00, $P = 0.99$).

IPASS was the first study to demonstrate the high incidence of EGFR mutation-positive tumours in female Asian patients who were never or light ex-smokers, with adenocarcinomas.

The presence of an EGFR mutation can be both a predictive and prognostic factor of improved efficacy and outcomes. We now have similar results from Korean[23] and Japanese trials[24], which also showed very positive results in patients with EGFR mutation-positive tumours who received gefitinib. The same results were recently presented with erlotinib *vs* carboplatin-gemcitabine in the OPTIMAL trial, (previously known as CTONG 0802)[25,26], where EGFR mutation-positive patients had median PFS on erlotinib of 13.1 mo *vs* 4.6 mo on chemotherapy (HR = 0.16, $P < 0.0001$). The Spanish Lung Cancer group demonstrated similar results in a phase Ⅱ trial[27].

In mutation-positive patients (exon 19 deletion and 21 point mutation), EGFR-TKIs are the treatment of choice in the first-line for metastatic NSCLC. Oral administration is more convenient and less toxic contributing to a better QOL and excellent efficacy in many patients. In the case of unknown mutation status, patients should receive chemotherapy treatment. Education on the necessity of an adequate tumour biopsy is of utmost importance for optimal patient management. Currently, there are no predictive markers for anti-VEGF therapy.

Maintenance therapy

A number of studies have evaluated regimens using either sequential or maintenance chemotherapy as post first-line treatment for NSCLC patients who have not experienced disease progression. A review of those studies suggests that the optimal regimen remains unclear[2,28].

Chemotherapy in maintenance

A phase Ⅲ trial[29] compared the efficacy and safety for docetaxel administered to patients either immediately after first-line gemcitabine-carboplatin or only at the time of disease progression. The study showed a statistically significant improvement in PFS of 3 mo for patients receiving immediate docetaxel therapy and a non-significant trend toward an improved OS. Ninety-five percent of patients in the immediate arm received docetaxel, but only 63% of patients in the delayed-therapy arm received docetaxel. When OS was compared only for patients who received docetaxel, median OS was 12.5 mo in both arms.

The JMEN trial evaluated maintenance pemetrexed plus best supportive care (BSC) against placebo plus BSC. With maintenance pemetrexed, the PFS in the overall patient population was 4.0 mo as compared with 2.0 mo for placebo (HR = 0.60, $P < 0.0001$)[30]; however, patients with squamous histology did not benefit from pemetrexed therapy. The trial excluded patients who had previously

Table 1 Efficacy (progression-free survival) outcomes of trials in the maintenance setting in patients with non small cell lung carcinoma

Trial	Treatment	*n*	Median PFS (mo)	HR
AVAiL[31]	Placebo	41	3.2	NR
	Bevacizumab 7.5 mg/kg	174	4.6	
	Bevacizumab 15 mg/kg	162	4.6	
ATLAS[32]	Bevacizumab + erlotinib	370	4.76	0.722
	Bevacizumab + placebo	373	3.75	$P = 0.0012$
SATURN[33]	Erlotinib	437	NR	0.71
	Placebo	447	NR	$P < 0.0001$
JMEN[30]	Pemetrexed	441	4.0	0.5
	Placebo	222	2.0	$P < 0.0001$

PFS: Progression-free survival; HR: Hazard ratio.

Table 2 Efficacy data in the second-line setting

Outcome	Erlotinib[41] (150 mg daily)	Docetaxel[38-40,46] (75 mg/m^2 every 3 wk)	Pemetrexed[40] (500 mg/m^2 every 3 wk)
RR (%)	8.9	6.7-8.8	9.1
Median duration of response (mo)	7.9	5.3-9.1	4.6
Median PFS (mo)	2.2	2.7-6	2.9
Median OS (mo)	6.7	5.7-7.9	8.3
1-year survival (%)	31	30-37	30
2-year survival (%)	13	0	0
Median OS (mo) in PS 0/1 patients with one prior regimen	9.4	9.1	9.4

PFS: Progression-free survival; OS: Overall survival; PS: Performance status.

received pemetrexed with cisplatin. The lack of a delayed pemetrexed arm means that it is difficult to ascertain the true benefit of immediate compared to second-line pemetrexed. Only 19% of patients in the placebo arm received pemetrexed in the second-line, raising the question of whether the observed survival benefit would have been maintained if more patients had received second-line pemetrexed. Patients on pemetrexed require folic acid and vitamin B12 to reduce treatment-related toxicities. The most frequent adverse events related to pemetrexed are neutropenia and fatigue.

Targeted therapies in maintenance

In all bevacizumab trials, bevacizumab was administered as a maintenance therapy, followed by first-line chemotherapy with bevacizumab, if there was no disease progression or unacceptable toxicity. In the maintenance phase of AVAIL, (Avastin in Lungs), there was a significant increase in PFS in the bevacizumab arm as compared with the placebo arm (4.6 mo *vs* 3.2 mo, Table 1)[31]. The Atlas trial demonstrated that the benefit is further improved with the addition of erlotinib (4.76 mo *vs* 3.75 mo, HR = 0.722)[32], but OS was not improved and the toxicity was more severe on the two-drug arm. In the SATURN trial, a 41% improvement in PFS was observed for erlotinib as compared with placebo[33]. In addition, maintenance with erlotinib demonstrated a survival benefit in all subgroups of patients, including those with squamous tumour pathology. This benefit was independent of EGFR mutation status[34]. For the mutation-positive patients, a HR = 0.1 for median PFS was unprecedented.

Future directions

A phase Ⅱ trial reported by Patel *et al*[35] demonstrated excellent results with first-line pemetrexed plus carboplatin and bevacizumab followed by maintenance with pemetrexed and bevacizumab in non-squamous NSCLC patients. The overall response rate was 55%, median PFS was 7.8 mo and OS was 14.1 mo. Another phase Ⅱ trial demonstrated that bevacizumab plus pemetrexed and oxaliplatin followed by bevacizumab maintenance achieved a median PFS of 7.8 mo and a median OS of 16.7 mo[36]. These trials suggest an improved efficacy when bevacizumab and pemetrexed are combined in different regimens. Phase Ⅲ trials are ongoing.

Clinical trial data in colorectal cancer patients suggest an advantage in maintaining clinical benefit by continuing bevacizumab beyond progression to keep VEGF levels down[37], in bevacizumab eligible patients.

Patients who are not eligible for bevacizumab and/or want a more convenient, oral treatment, causing mainly rash or diarrhoea, can be maintained by erlotinib, which is also effective in squamous histology, unlike pemetrexed. For non-squamous histology, depending on patient preference or ineligibility for bevacizumab, pemetrexed also remains an option.

Palliative therapies, especially early prevention of skeletal-related events, such as fractures, spinal cord compression, radiotherapy, and surgery to bone should be an integral component of active treatments[38,39].

SECOND-LINE THERAPY

Chemotherapy in second-line

Several chemotherapy agents, including docetaxel and pemetrexed, have demonstrated efficacy in the second-line treatment of NSCLC patients[40-43]. Pemetrexed is approved for non-squamous histology only. Both drugs offer similar efficacy in randomized, phase Ⅲ trials[42], with median OS of 8.3 mo for docetaxel and 7.9 mo for pemetrexed, however, pemetrexed has a milder toxicity profile than docetaxel[41].

Targeted therapies in second-line

Erlotinib is an EGFR-TKI that suppresses intracellular signalling pathways, which promote cell growth and proliferation[44,45]. Unlike chemotherapy, it causes no cumulative hematologic toxicities, allowing for a longer treatment duration. The toxicities associated with chemotherapy allow for only a limited number of cycles, median of approximately 4 cycles. Table 2 compares clinical data for erlotinib, docetaxel, and pemetrexed.

In a randomized, placebo-controlled study (NCIC BR.21), erlotinib demonstrated improvement in median

OS (6.7 mo *vs* 4.7 mo) and QOL across all subgroups[43,46]. Fifty percent of patients were treated in second-line, and 50% in third-line; some patients even had PS of 3.

The safety and efficacy of erlotinib were confirmed in the phase Ⅳ trial, TRUST (TaRceva LUng Cancer Survival Treatment), in a broad patient population[47], where median OS was 8.1 mo, and 1-year survival was 38.6%.

Gefitinib, another EGFR-TKI, failed to demonstrate a survival advantage in the overall population of the phase Ⅲ trial, ISEL (Iressa Survival Evaluation in Lung Cancer), where patients had to be refractory to previous chemotherapy. A phase Ⅱ study of a single-agent, sorafenib (targeting mainly angiogenesis), in second-line suggests only modest benefits and some specific toxicity, such as hand-foot syndrome[48]. Vandetanib (ZACTIMA), targeting VEGF receptor and EGFR, has demonstrated only a modest benefit[49-51] in phase Ⅲ second-line trials alone or in combination with pemetrexed or docetaxel; and was withdrawn from the market for NSCLC treatment.

A practical approach in second-line

A good response to first-line chemotherapy may warrant further chemotherapy in second-line. A meta-analysis of single agents *vs* doublet chemotherapy demonstrated improvement in response rate, but it did not translate into a PFS or OS benefit, only being associated with an increased toxicity[52]. If patients tolerated first-line chemotherapy poorly, an EGFR inhibitor may be the preferred choice for second-line.

Non-inferiority in terms of OS for gefitinib compared with docetaxel, was demonstrated in the phase Ⅲ trial INTEREST (Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere)[53]. Non-inferiority was shown regardless of a patient's EGFR protein expression, EGFR gene mutation, or K-RAS gene mutation status. The only advantage for OS was for patients who received docetaxel in third-line treatment. Given the lack of difference in clinical benefit relating to the sequence of chemotherapy *vs* EGFR-TKI in the second and third lines (INTEREST), as well as reduced toxicity and easy, convenient oral administration (sometimes for longer periods of time), EGFR-TKIs are preferred second-line agents for NSCLC. Obtaining EGFR (exon 19 and 21) mutation status of the tumour for second-line treatment of NSCLC is not a necessity. Numerous randomized trials for second-line treatments of NSCLC are ongoing with different targeted agents. Patients who received EGFR-TKIs in first-line as their tumours were positive for EGFR mutations, could receive a platinum doublet in second-line, if their PS and comorbidities permit. More data are needed for this patient population. We now have data from many trials with bevacizumab and EGFR-TKIs, see Table 3.

THIRD-LINE TREATMENT

A number of trials are investigating the role of anticancer therapies in the third or fourth-line setting. The phase Ⅲ Zephyr trial (Zactima Efficacy trial for NSCLC Patients with HistorY of EGFR and chemo-Resistance), investigated the role of Vandetanib in the third and fourth-line setting. Median PFS was significantly prolonged - 1.9 mo on Vandetanib *vs* 1.8 mo on placebo ($P < 0.0001$, HR = 0.63)[54].

BIBW 2992 (Afatinib), a dual irreversible inhibitor of EGFR and Her-2 demonstrated encouraging results in a randomized, phase Ⅲ trial (Lux Lung 1), involving 585 patients who had progressed after 1-2 chemotherapy regimens (one had to be platinum-based) and who had to be at least 3 mo on EGFR-TKI without disease progression. The patients received afatinib 50 mg po daily plus BSC or BSC plus placebo (randomization was 2:1). Median time on EGFR-TKI was 10.2 mo, 81% patients were receiving EGFR-TKIs for more than 24 wk. Complete or partial response on prior EGFR-TKI treatment was 45% suggesting a very high tumour EGFR mutation rate. Afatinib extended median PFS, tripling it over PFS with placebo (3.3 mo *vs* 1.1 mo, $P < 0.001$, HR = 0.38)[55], however, median OS, the primary endpoint, was not significantly different, 10.78 mo with BSC plus afatinib *vs* 11.96 mo with BSC plus placebo (HR = 1.077, $P = 0.7428$). The disease control rate was higher on afatinib (58% *vs* 18%, $P < 0.0001$). Moreover, afatinib significantly improved cough, dyspnea and pain, and delayed the time of deterioration of these symptoms[54]. The main side effects as expected were diarrhoea and rash, which were manageable. OS was confounded by further lines of treatment and their imbalance. Seventy nine percent of patients in the placebo arm received further chemotherapies or targeted agents. One hundred and forty four patients in the afatinib arm and 43 patients in the placebo arm did not receive further lines as no treatment was available in these centres, and here OS favoured the afatinib arm ($P = 0.02$, HR = 0.65). Patients who clinically benefited from prior EGFR-TKI (i.e. response rate, DCR > 6 mo) had PFS 4x longer on afatinib *vs* placebo (4.4 mo *vs* 1.1 mo) and there was a trend for better OS (HR = 0.9).

A phase Ⅲ trial of sorafenib (a multikinase inhibitor) *vs* placebo, the MISSION trial (Monotherapy Administration of Sorafenib in patientS with non-small cell Lung cancer), in third or fourth-line therapy has finished accrual and results are expected soon. Combining an insulin-like growth factor (and receptor) inhibitor with erlotinib to try to prevent development of resistance to erlotinib is also under investigation.

Practical approach in third-line

Erlotinib is a viable third-line treatment option for patients who have not yet received it. In spite of an exquisite sensitivity of EGFR mutation-positive tumours to EGFR-TKIs such as erlotinib or gefitinib, eventually all patients progress, as they develop resistance to EGFR-TKIs. The most frequent mutation is T790M on exon 20, and is found in about 50% of such patients. Afatinib showed preclinical evidence of activity for this mutation

Table 3 Selected trials of erlotinib and bevacizumab

Study	Phase	*n*	Eligibility	Regimen	Line of therapy	Primary endpoint
PASSPORT (AVF3752g)	II	110	Previously treated or untreated non-squamous NSCLC with treated CNS metastases	Chemo or erlotinib followed by bev	First/second	Grade ≥ 2 symptomatic CNS haemorrhage
BRAIN (AVF21823)	II	115	Stage Ⅳ non-squamous NSCLC with asymptomatic brain metastases in first and second line	First line: bev + carbo/pac Second line: bev + erlotinib	First/second	PFS
EAGLES	II	78	Patients aged > 70 yr without important comorbidities	Bev + gem or bev + gem/cis	First	PFS at 6 mo
ML21896	II	~250	Patients aged ≥ 65 yr with advanced metastatic or recurrent non-squamous NSCLC	Bev + pem or bev + pem/carbo	First	Proof of non-inferiority of bev + pem
BRIDGE (AVF2744g)	I/II	40	Previously untreated squamous NSCLC	Bev + carbo/pac	First	Grade ≥ 3 pulmonary haemorrhage
ABIGAIL (BO21015)	II	~300	Locally advanced, metastatic or recurrent non-squamous NSCLC	Bev + carbo/gem or carbo/pac	First	Correlation of biomarkers with response
MIMEB (ML21803)	II	40	Histologically confirmed advanced non-squamous NSCLC stage ⅢB/Ⅳ	Bev + erlotinib	First	Evaluate accuracy of FDG-/FLT-PET and DCE-MRI for early prediction of non-progression
EURTAC	III	146	EGFR mutation-positive NSCLC	Erlotinib	First	PFS in patients with
SATURN (BO18192)	III	1949	Previously untreated advanced NSCLC	Erlotinib	First	PFS in all patients and in patients with EGFR IHC+ tumours
RADIANT		945	Advanced NSCLC	Erlotinib *vs* placebo	Adjuvant	DFS
FASTACT-2	III	450	Asian patients with previously untreated advanced NSCLC	Erlotinib + chemo *vs* placebo + chemo	First line	PFS
ATLAS (AVF3671f)	III	1150	Previously untreated advanced NSCLC	Bev + carbo/pac, gem/cis or carbo/doc) Non-progressing patients randomized (1:1) to bev + erlotinib or bev + placebo	First line maintenance	PFS
TARGET	II	428	EGFR mutation-positive NSCLC	Erlotinib	First	PFS
TORCH	III	900	Previously untreated advanced NSCLC	First-line erlotinib second-line gem/cis *vs* first-line gem/cis second-line erlotinib	First/second	OS

NSCLC: Non-small cell lung cancer; CNS: Central nervous system; bev: Bevacizumab; carbo: Carboplatin; pac: Paclitaxel; PFS: Progression-free survival; gem: Gemcitabine; cis: Cisplatin; pem: Pemetrexed; FDG: [18F]-2-fluoro-deoxy-D-glucose; FLT: F-fluorodeoxythymidine; PET: Positron emission tomography; DCE-MRI: Dynamic contrast-enhanced magnetic resonance imaging; EGFR: Epidermal growth factor receptor; IHC: Immunohistochemistry; DFS: Disease-free survival; chemo: Chemotherapy; doc: Docetaxel; OS: Overall survival.

and Lux Lung 1 showed significant activity of afatinib, especially in patients with a high possibility of EGFR mutations on the basis of clinical criteria. Thus, afatinib is likely to be a possible option for third or fourth line treatment of metastatic NSCLC patients. Lux Lung 2 (60 patients in first line, and 60 patients in second-line, only EGFR mutation-positive NSCLC) showed very exciting results, median PFS of 15 mo, median OS of 24 mo for patients with EGFR exon 19 and 21 mutations.

Two phase Ⅲ trials in EGFR mutation-positive patients with adenocarcinoma treated in first-line, comparing afatinib to cisplatin-pemetrexed, are ongoing.

Only 3%-5% of patients with NSCLC have the ALK fusion gene. Crizotinib is an oral, potent and selective small-molecule ATP-competitive inhibitor of ALK and MET kinases and their oncogenic variants. Overall response rate was 56%, DCR at 8 wk was 88% and median PFS was 9.0 mo in heavily pre-treated NSCLC patients[56].

Trials are now ongoing in first-line treatment, comparing crizotinib to pemetrexed/cisplatin or carboplatin in a phase Ⅲ study of non-squamous NSCLC and in second-line comparing crizotinib to pemetrexed or docetaxel again in a phase Ⅲ study[6].

CONCLUSION

The main goal should be to provide the best possible treatment in terms of both efficacy and safety in each line of therapy. As compared with chemotherapeutic agents, targeted agents may offer reduced toxicity, especially with prolonged use. By increasing the agent's specificity, and possibly combining different agents in order to target different pathways, we will increase the treatment efficacy[57]. New agents, such as PARP inhibitors for squamous cancers, and IGFR, HDAC, HSP 90 and C-MET inhibitors are being tested in clinical trials, especially in combination with the already established targeted agents or with chemotherapy.

Predictors of response may help to guide individual treatment decisions. We need to identify the biomarkers of response and resistance (old and newly developed) at every step, and every line of treatment. A personalized,

targeted approach is the future of treatment in all lines, and a re-biopsy of tumours will be required for analysis of biomarkers, including newly developed markers of resistance to EGFR-TKIs, but also sensitivity to other agents, such as afatinib. Analysis of circulating tumour cells and blood biomarkers to define predictors of tumour response and treatment benefit is needed for the future.

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