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Efficacy and Safety of Gefitinib or Platinum plus Taxane in Egfr-Mutant Advanced Non-Small Cell Lung Cancers: A Meta-Analysis of First-Line Randomized Controlled Trials*

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ABSTRACT

Purpose: The discovery of EGFR mutations renewed interest in lung cancer translational research since EGFR-dependent pathway plays an important role in the development and progression of human epithelial cancers, including non-small cell lung cancer (NSCLC). The present meta-analysis was performed to review the recent advances with the selective oral EGFR-TK inhibitor gefitinib among EGFR mutation positive patients with NSCLC. **Methods:** Using the keywords "gefitinib" and "lung cancer" MEDLINE was searched. The primary reports of interest were the randomized controlled trials in NSCL published in peer-reviewed journals. Three recent studies concerning the effect of gefitinib in NSCLC were identified to be relevant for the meta-analysis based on their similarity in terms of study design. PFS and objective response rate (ORR) in gefitinib and platinum/taxane combination were compared by the Hazard ratio (HR) or Odds Ratio (OR) of meta-analysis. **Results:** The HR (95% CI) of the meta-analysis of 0.41 (0.34 - 0.49) demonstrated that in patients EFGR mutation positive patients, PFS was significantly longer among those who received gefitinib compared to platin derivative/taxane combination. Furthermore, OR of the meta-analysis for ORR was 3.83 (2.72 - 5.40). While hematological toxicity was observed in the majority of the taxane/platinum group, major adverse events in gefitinib patients were skin rashes/acnea, dry skin, elevated liver enzymes and diarrhea. **Conclusion:** This meta-analysis strongly confirms the efficacy and better tolerability of gefitinib in EGFR positive NSCLC, and the importance of EGFR mutation testing in order to plan first-line treatment in routine clinical practice in NSCLC.

Keywords: Gefitinib; EGFR Mutation; Lung Cancer; Meta-Analysis

1. Introduction

In recent years, various molecular targeted therapies have been developed for the treatment of advanced NSCLC in an attempt to improve prognosis. One such target has been the EGFR, which is frequently expressed at high levels in tumor tissue compared to the corresponding healthy tissue [1]. Accordingly, in the last decade, two small molecules, orally active, selective and reversible EGFR-tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib have been developed for the treatment of NSCLC [2].

In fact, increased demand to identify sub-sets of NSCLC patients to improve outcomes in this heterogeneous disease having a median survival barely exceeding 12 months [3], great efforts in clinical and laboratory research in recent years led to a better knowledge of pre-dictive factors of the efficacy of EGFR-TKIs [4].

Identification of somatic mutations in the tyrosine kinase domain of the EGFR in patients with NSCLC by three groups of investigators in 2004 [5-7] revealed almost ubiquitous presence of these mutations in patients who had radiographic and clinical responses to gefitinib [4-6].

Accordingly, subsequent population-based efforts to sequence EGFR in NSCLC have consistently identified EGFR mutations in an enriched cohort of women, non-smokers, adenocarcinomas and East Asians including small inframe deletions around the conserved LREA motif of exon 19 (residues 747 - 750), followed by a single point mutation in exon 21-L858R as the most prevalent EGFR mutations [4]. In particular, increasing evidence has been accumulated, supporting a strong predictive role of EGFR gene mutation in tumor cells. In parallel, EGFR inhibition strategy, that was originally limited to patients

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who had already failed previous standard treatment, has been tested as first-line strategy [2].

As reviewed recently [2], the background of gefitinib treatment has been based on the ground of randomized clinical trials (RCTs) conducted in unselected patients with advanced NSCLC pretreated with chemotherapy as second line treatment [8-14], as first-line treatment of unselected patients in chemotherapy naïve patients [15-19], small studies concerning gefitinib as first-line treatment of patients selected for the presence of EGFR mutation [20-24], or selected according to other clinical or molecular putative predictive factors [25,26] followed by randomized phase III trials [27-30] conducted in East Asian countries comparing gefitinib vs. platinum-based chemotherapy as first-line treatment in patients with advanced NSCLC (**Table 1**).

Besides gefitinib, two other anti-EGFR-TKI including erlotinib [31] and afatinib [32,33] were reported to be superior to chemotherapy in terms of PFS as first-line treatment of patients with EGFR-mutation positive tumors [2]. In a randomised trial (OPTIMAL, CTONG-0802) conducted in China [31], non-small-cell lung cancer patients with a confirmed activating mutation of

EGFR (exon 19 deletion or exon 21 point mutation) received either oral erlotinib or gemcitabine plus carboplatin in the first line setting. Median progression-free survival was significantly longer in erlotinib-treated patients than in those on chemotherapy [hazard ratio (HR) 0.16 (0.10 - 0.26); p < 0.0001). In the interim analysis of EURTAC trial in Asia, the first line erlotinib showed significant benefit of PFS over standard chemotherapy in EGFR-mutated cases [HR = 0.42 (0.27 - 0.64), p < 0.0001] [34]. No overall survival differences could be detected in these trials. Since patients included in OPTIMAL-CTONG-0802 trial received either oral erlotinib or gemcitabine plus carboplatin rather than platinum/taxane combination in the first line setting, the present meta-analysis included only gefitinib trials.

Providing a basis for the present meta-analysis, RCTs comparing gefitinib versus standard first-line chemotherapy of platinum/taxane combination for advanced NSCLC demonstrated a striking progression-free survival (PFS) prolongation for patients receiving gefitinib, although no difference in overall survival (OS) could be detected, possibly related to the crossover design as reported in a recent meta-analysis [27,29,30].

Table 1. A brief recent history of gefitinib trials in NSCLC.

Year	Development
2003	FDA approval for gefitinib based on 2 phase II trials [8,41].
2003	IDEAL I and IDEAL II phase II studies had objective response rate of 12% - 18% and demonstrated favorable tolerability [8,9].
2004	Iressa NSCLC Trial Assessing Combination Treatment (INTACT) -1 and -2, failed to show a significant survival benefit with the addition of gefitinib to chemotherapy (either cisplatin/gemcitabine or carboplatin/paclitaxel) [15,16].
2005	Gefitinib was approved in other countries. Phase III ISEL trial led to restriction of gefitinib use in USA that showed no statistical significance in overall survival [10].
2006	A subgroup analysis of the ISEL study revealed a significant survival benefit in two patients who had never smoked or who were of Asian ethnicity compared with those who received best supportive care. Biomarker analyses of samples from ISEL suggested that high EGFR gene copy number was a predictor of clinical benefit from gefitinib [42].
2008	Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST) trial demonstrated non-inferiority of gefitinib for OS in pretreated patients but with a more favorable tolerability profile and significantly improved quality of life [14].
2008	Phase II study Iressa in NSCLC versus Vinorelbine Investigation in the Elderly (INVITE) comparing gefitinib with vinorelbine in elderly chemonaive patients failed to demonstrate a statistically significant efficacy benefit for first-line gefitinib in these patient settings [43].
2009	Iressa NSCLC Trial Evaluating Poor Performance Status Patients (INSTEP) comparing gefitinib with best supportive care in patients with poor performance status failed to demonstrate a statistically significant efficacy benefit for first-line gefitinib [44].
Randomized Controlled Phase III Trials evaluating first-line gefitinib vs standard platinum-base chemotherapy	
2009	Iressa Pan-Asia Study (IPASS) met its primary endpoint of demonstrating non-inferiority and, furthermore, demonstrated the superiority of first-line gefitinib compared with standard carboplatin/paclitaxel in PFS (Overall HR = 0.74; 95% CI: 0.65 - 0.85; p < 0.001; HR in EGFR mutation-positive patients = 0.48; 95% CI: 0.36 - 0.64) [27].
2010	In WJTOG3405 trial by West Japan Oncology Group, patients with EGFR mutations were included, and had longer PFS if they were treated with gefitinib compared to cisplatin/docetaxel (HR = 0.49; 95% CI: 0.34 - 0.71; p < 0.002) [29].
2010	In the RCT by North-East Japan Study Group, in patients who were selected on the basis of EGFR mutations, gefitinibe improved PFS with acceptable toxicity, as compared with carboplatin/paclitaxel (HR = 0.30; 95% CI: 0.22 - 0.41; p < 0.001) [30].

Since there is no debate on the clinical superiority of gefitinib, a meta-analysis seems to be useful for consolidation of the existing knowledge by increasing the statistical power rather than resolving conflicting areas by providing HR for PFS and OS that may help to draw the attention of the physicians and the health authority to consider EGFR mutation test and gefitinib use into routine practice of NSCLC. Therefore, the present meta-analysis was focused on data from EGFR mutation-positive patients in 3 recent phase III RCTs with homogenous design and same TKI in Asian population [27,29,30] that consistently support the role of gefitinib treatment option in advanced NSCLC compared to platinum/taxane combination. Both the efficacy and safety of gefitinib or chemotherapy in the first-line treatment of EGFR mutated NSCLC were evaluated in this meta-analysis.

2. Materials and Methods

MEDLINE was searched using the keyword "gefitinib" and "lung cancer". Of more than 1900 published reports retrieved, older studies and studies with diverse methodology were excluded while the primary reports of interest were the RCTs in NSCLC published in peer-reviewed journals since 2005 after which gefitinib use was intensified. Four recent studies concerning the effect of first-line gefitinib vs standard chemotherapy in advanced NSCLC were identified to be relevant for the meta-analysis based on their similarity in terms of study design. However, one of these studies was also excluded since results have not been yet published in a peer-reviewed journal yet, but only its abstract could be accessed [28]. Furthermore, the standard therapy arm (carboplatin/gemcitabine) was different that the other 3 included RCT (carboplatin/taxane) [27,29,30].

Additionally, since the primary endpoint of all three

selected trials was progression free survival while the overall survival results were only reported in two of the selected trials, present meta-analysis was based only on PFS rather than OS. Accordingly, overall survival was reported as 0.78 (95% CI 0.50 - 1.20) for OS in EGFR-M(+) subgroup by Mok *et al.*, 2009 [27] and not as HRs but as survival time and 2 year survival rate of 30.5 vs 23.6 months; and 61.4% vs 46.7% for gefitinib and carboplatin-paclitaxel patients, respectively (p = 0.31) by Maemondo *et al.* 2010 [30], while not reported by Mitsudomi *et al.*, 2010 [29].

Characteristics of trial design and the main outcomes are summarized in **Table 2**. The primary efficacy measure was PFS at all 3 studies included in the meta-analysis. Pooled HR for PFS and Odds Ratio (OR) for objective response rate (ORR) as efficacy endpoints are calculated; and adverse events are listed recorded at the RCTs included at the meta-analysis. OS at two studies included in the meta-analysis. Regarding toxicity data the toxicity analysis was actually based on a data obtained for EGFR mutated population in two trials [29,30] and in an unselected population of patients including all but not only EGFR-mutated patients in one trial [27].

Statistical Analysis

"Comprehensive Meta-Analysis version 2" software program (USA) was used. For the effect estimates, HRs or ORs with the 95% confidence intervals (CIs) obtained in EGFR mutation-positive patients were used for the meta-analysis.

3. Results

Selected Trials

Three randomized phase III trials comparing gefitinib to

Table 2. Summary of RCTs included in this meta-analysis

Ref #	Inclusion criteria	Study arm	Number (%) of patients with EGFR-M	Number (%) of never smokers	Number (%) of patients with stage IIIB/IV disease	Number (%) of female patients
27[*]	Age > 18 years NSCLC (stage IIIb or IV) Non-smoker/former light smoker Chemotherapy -naive	Gefitinib	132 (59.2)	124 (93.9)	132 (100.0)	108 (81.8)
		Carboplatin/Paclitaxel	129 (60.3)	122 (94.6)	129 (100.0)	103 (79.8)
29	Age < 75 WHO PS 0 - 1 Activating EGFR-M (exon 19 deletion or L858R inexon 21)	Gefitinib	86 (100.0)	61 (70.9)	51 (59.3)	59 (68.6)
		Cisplatin/Docetaxel	86 (100.0)	57 (66.3)	50 (58.1)	60 (69.8)
30	Age < 75 ECOG PS 0 - 2 Sensitive EGFR-M (absence of resistant EGFR mutation T790 M)	Gefitinib	114 (100.0)	75 (65.8)	103 (90.4)	72 (63.2)
		Carboplatin/Paclitaxel	114 (100.0)	66 (57.9)	105 (92.1)	73 (64.0)

ECOG PS: Eastern Cooperative Oncology Group Performance status; EGFR-M: Epithelium growth factor receptor mutation; NSCLC: Non-small cell lung cancer; WHO: World Health Organisation; [*]Data for EGFR-M (+) patients are obtained from the Supplementary Appendix of the article that can be accesses via www.nejm.org.

platinum-based chemotherapy in patients with advanced NSCLC eligible for first-line treatment were included in the present meta-analysis [27,29,30].

Being conducted in East Asian countries, patients assigned to the experimental arm received oral gefitinib at the standard dose (250 mg daily) while the chemotherapy arm received different platinum-based doublets including carboplatin plus a taxane (paclitaxel in 2 trials [27,30], docetaxel in 1 trial [29].

In relation to the previous evidence demonstrating high frequency of EGFR mutations, and high activity of gefitinib in NSCLC patients with these characteristics, inclusion criteria of one of the three trials [27] was based on a clinical selection according to clinical factors known to be associated with higher prevalence of EGFR mutation (adenocarcinoma, including bronchioloalveolar carcinoma, and either never smokers or former light-smokers). Of 1217 patients included [27], 261 patients were determined to be EGFR mutation positive. The remain-

ing two trials [29,30] were based on biomarker-driven selection that only patients with EGFR mutation-positive tumor were considered to be eligible. All patients (172 and 228 patients, respectively) included were EGFR mutation-positive with respect to inclusion criteria. Accordingly, after exclusion of patients without mutations, a total of 661 patients with EGFR mutation from three trials were included in the present meta-analysis (332 allocated to gefitinib, and 329 to platinum/taxane arm).

Progression free survival: The HR (95% CI) of the meta-analysis of 0.41 (0.34 - 0.49; $p < 0.001$) demonstrated that in patients who were positive for the EFGR gene mutation, PFS was significantly longer among those who received gefitinib than among those who received platinum derivative/taxane combination. In other words, a 2.44 times longer PFS time was obtained with gefitinib in these patients (**Table 3** and **Figure 1**). Based on disease stage [27,29] and gender [29,30] related evaluation, hazard ratios (HRs) of gefinib treatment was lower in

Table 3. Effect estimates obtained at the individual RCTs and the meta-analysis in EGFR mutation (+) patients.

Ref #	Objective Response Rate		
	%	OR (95% CI)	OR of the meta-analysis (95% CI)
27	71.2 vs 47.3, $p < 0.001$	2.75 (1.65 - 4.60), $p < 0.001$	
29	62.1 vs 32.2, $p < 0.001$	3.45 (1.61 - 7.38), $p < 0.001$	3.83 (2.72 - 5.40) $p < 0.001$
30	73.7 vs 30.7, $p < 0.001$	6.22 (3.55 - 11.35), $p < 0.001$	

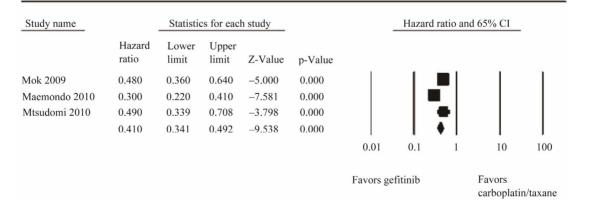|		Progression Free Survival		
	Ref #	Months	HR (95% CI)	HR of the meta-analysis (95% CI)
All EGFR mutation (+) patients	27	9.6 vs. 6.3; $p < 0.001$	0.48 (0.36 - 0.64)	
All EGFR mutation (+) patients	29	9.2 vs 6.3; $p < 0.001$	0.49 (0.34 - 0.71)	0.41 (0.34 - 0.49), $p < 0.001$
All EGFR mutation (+) patients	30	10.8 vs 5.4; $p < 0.001$	0.30 (0.22 - 0.41)	
Patients with Stage IIIB/IV disease	27	9.6 vs. 6.3; $p < 0.001$	0.48 (0.36 - 0.64)	
Patients with Stage IIIB/IV disease	29	-	0.33 (0.20 - 0.54)	0.44 (0.34 - 0.56), $p < 0.001$
Patients with Stage IIIB/IV disease		-	-	
Females	27	-	-	
Females	29	-	0.42 (0.27 - 0.65)	0.59 (0.46 - 0.75), $p < 0.001$
Females	30	6.5 vs 6.0; $P = 0.01$	0.68 (0.5 - 0.92)	

Figure 1. Forest plot using boxes to represent the effect size and relative weights of gefitinib against platinum/taxane doublet.

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patients with Stage III/IV patients (HR = 0.44 (0.34; 0.56; p < 0.001) and in females (HR = 0.59 (0.46; 0.75; p < 0.001) (**Table 3**). Nonetheless, no gender comparison was reported in the trial by Mok *et al.* 2009 [27] includeing patients in stage IIIb/IV, while no disease stage comparison was evident in the trial by Maemondo *et al.*, 2010 [30] which stated that women had significantly longer PFS than men (median 6.5 vs 6.0 months) whereas HRs for PFS for gefitinib vs chemotherapy in males was not provided. HR for PFS in early stage (post-op) group was 0.57 (95% CI 0.31 - 1.05), in stage IIIb/IV group was 0.33 (95% CI 0.20 - 0.54) in the trial by Mitsudomi *et al.*, 2010 [29] which stated HR for PFS in males to be 0.67 (95% CI 0.34 - 1.33) and in females to be 0.42 (95% CI 0.27 - 0.65).

Objective Response Rate: The OR (95% CI) for the ORR of the meta-analysis of 3.83 (2.72 - 5.40; p < 0.001) in patients who were positive for the EFGR gene mutation (**Table 3**).

Safety: The safety results of the individual RCTs showed that hematological toxicity, fatigue, nausea and alopecia were the most frequent adverse events in the taxane/platinum group, while major adverse events in gefitinib patients were skin rashes/acnea, dry skin, elevated liver enzymes and diarrhea (**Tables 4** and **5**).

4. Discussion

The present meta-analysis provides the magnitude of benefit obtained with the EGFR-TKI gefitinib when used as front-line treatment in advanced, EGFR-M+, NSCLC patients. The HR obtained with this meta-analysis more strongly supports the efficacy of gefitinib, and stresses on the importance of EGFR mutation test and gefitinib use in routine practice of NSCLC safely.

Report of EGFR mutations in exons 19 or 21 amongst patients responding to gefitinib, as compared to no mutation found in non-responders [5-7,35] triggered studies

Table 4. Adverse events observed at the individual randomized controlled trials included in this meta-analysis.

	Gefitinib (n (%))						Platinum/Taxane (n (%))					
	Ref [27] (n = 607)		Ref [29] (n = 87)		Ref [30] (n = 114)		Ref [27] (n=589)		Ref [29] (n = 88)		Ref [30] (n = 113)	
Adverse event	All	CTC grade ≥ 3	All	CTC grade ≥ 3	All	CTC grade ≥ 3	All	CTC grade ≥ 3	All	CTC grade ≥ 3	All	CTC grade ≥ 3
Non-hematological toxicity												
Rash or acne	402 (66.2)	19 (3.1)	74 (85.1)*	2 (2.3)	81 (71.1)	6 (5.3)	132 (22.4)	5 (0.8)	7 (79.5)	0 (0.0)	25 (22.1)	3 (2.7)
AST	NA	NA	61 (70.1)*	14 (16.1)	63 (55.3)	30 (26.3)	NA	NA	17 (19.3)	1 (1.1)	37 (32.7)	1 (0.9)
ALT	NA	NA	61 (70.1)*	24 (27.6)	NA	NA	NA	NA	35 (39.8)	2 (2.3)	NA	NA
Dry skin	145 (23.9)	0 (0.0)	47 (54.0)*	0 (0.0)	NA	NA	17 (2.9)	0 (0.0)	3 (34.1)	0 (0.0)	NA	NA
Diarrhea	283 (46.6)	23 (3.8)	47 (54.0)	1 (1.1)	39 (34.2)	1 (0.9)	128 (21.7)	8 (1.4)	35 (39.8)	0 (0.0)	7 (6.2)	0 (0.0)
Fatigue	NA	NA	34 (39.1)*	2 (2.3)	12 (10.5)	3 (2.6)	NA	NA	73 (83.0)	2 (2.3)	31 (27.4)	1 (0.9)
Paronychia	828 (13.5)	2 (0.3)	28 (32.2)*	1 (1.1)	NA	NA	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	NA	NA
Stomatitis	103 (17.0)	1 (0.2)	19 (21.8)	0 (0.0)	NA	NA	51 (8.7)	1 (0.2)	13 (14.8)	0 (0.0)	NA	NA
Nausea	101 (16.6)	2 (0.3)	15 (17.2)*	1 (1.1)	NA	NA	261 (44.3)	9 (1.5)	83 (94.3)	3 (3.4)	NA	NA
Vomiting	78 (12.9)	1 (0.2)	NA	NA	NA	NA	196 (33.3)	16 (2.7)	NA	NA	NA	NA
Constipation	73 (12.0)	0 (0.0)	14 (16.1)*	0 (0.0)	NA	NA	173 (29.4)	1 (0.2)	39 (44.3)	0 (0.0)	NA	NA
Anorexia	133 (21.9)	9 (1.5)	NA	NA	17 (14.9)	6 (5.3)	251 (41.6)	16 (2.7)	NA	NA	64 (56.6)	7 (6.2)
Pruritus	118 (19.4)	4 (0.7)	NA	NA	NA	NA	74 (12.6)	1 (0.2)	NA	NA	NA	NA
Alopecia	67 (11.0)	0 (0.0)	8 (9.2)*	0 (0.0)	NA	NA	344 (58.4)	0 (0.0)	67 (76.1)	0 (0.0)	NA	NA
Arthralgia	39 (6.4)	1 (0.2)	NA	NA	3 (26.3)	1 (0.9)	113 (19.2)	6 (1.0)	NA	NA	54 (47.8)	8 (7.1)
Neuropathy	66 (10.9)	2 (0.3)	7 (8.0)*	1 (1.1)	1 (0.8)	0 (0.0)	NA	NA	23 (26.1)	0 (0.0)	63 (55.8)	7 (6.2)
Hematological toxicity												
Leucopenia	NA	9 (1.5)	13 (14.9)*	0 (0.0)	NA	NA	NA	202 (35.0)	82 (93.2)	43 (48.9)	NA	NA
Thrombocytopenia	NA	NA	12 (13.8)*	0 (0.0)	8 (7.0)	0 (0.0)	NA	NA	29 (33.0)	0 (0.0)	32 (28.3)	4 (3.5)
Neutropenia	NA	22 (3.7)	7 (8.0)*	0 (0.0)	7 (6.1)	1 (0.9)	NA	387 (67.1)	81 (92.0)	74 (84.1)	87 (77.0)	74 (65.5)
Anemia	NA	13 (2.2)	33 (37.9)*	0 (0.0)	21 (18.4)	0 (0.0)	NA	61 (10.6)	79 (89.8)	15 (17.0)	73 (64.6)	6 (5.3)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTC: National Cancer Institute Common Tehcnology Criteria, *p < 0.001 compared to platinum/taxane group; NA: not available. Events are included if they occurred in at least 10% of patients in each treatment group.

Table 5. Odds ratios of the meta-analysis for all grades of adverse events in gefitinib vs platinum/taxane treated patients.

	Odds ratio	%95 Confidence interval	p
Non-hematological toxicity			
Rash or acne	7.98	6.35 - 10.04	<0.001
AST	4.19	2.74 - 6.43	<0.001
Dry skin	12.56	7.80 - 20.23	<0.001
Diarrhea	3.09	2.47 - 3.87	<0.001
Fatigue	0.20	0.12 - 0.33	<0.001
Paronychia	30.52	5.86 - 158.92	<0.001
Stomatitis	2.05	1.48 - 2.84	<0.001
Nausea	0.21	0.16 - 0.27	<0.001
Constipation	0.31	0.24 - 0.41	<0.001
Anorexia	0.33	0.26 - 0.42	<0.001
Alopecia	0.08	0.06 - 0.11	<0.001
Arthralgia	0.28	0.20 - 0.40	<0.001
Neuropathy	0.47	0.35 - 0.64	<0.001
Hematological toxicity			
Thrombocytopenia	0.26	0.15 - 0.45	<0.001
Neutropenia	0.01	0.01 - 0.03	<0.001
Anemia	0.10	0.06 - 0.16	<0.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTC: National Cancer Institute Common Tehcnology Criteria [*]p < 0.001 compared to platinum/taxane group.

that provided preliminary evidence about predictive factors of gefitinib efficacy. Accordingly the frequency of somatic mutations within the tyrosine kinase domain of the EGFR gene was shown to be low in unselected Western patients with advanced NSCLC, but, interestingly, these mutations appeared to be much more frequent in Japanese and East Asian population [2]. Furthermore, it was rapidly evident that some clinical or pathological characteristics are associated with higher prevalence of mutation: in detail, EGFR mutation is more frequent in never smokers, in women, and in patients with adenocarcinoma [2]. Based on this evidence, several small trials were conducted testing gefitinib as first-line treatment of patients selected for the presence of EGFR mutation [20-24], or selected according to other clinical or molecular putative predictive factors [25,26] followed by randomized phase III trials [27-30] conducted in East Asian countries comparing gefitinib vs. platinum-based chemotherapy as first-line treatment in patients with advanced NSCLC.

Accordingly, indicating a high-level evidence, coming from four prospective, randomized phase III trials [27-30], two of which were conducted specifically in patients with tumor harbouring EGFR mutation [29,30], in patients with advanced NSCLC selected for the presence of EGFR mutation, the administration of first-line gefitinib,

compared to standard platinum-based chemotherapy seems to be associated with longer PFS, higher ORR, a more favorable toxicity profile and better quality of life. Likewise, an estimate of the magnitude of benefit was reported with EGFR-TKI (gefitinib and erlotinib) in a recent meta-analysis, when used as front-line treatment in advanced, EGFR-M+, NSCLC patients. In this setting, EGFR-TKI has been considered to provide an unusually large PFS benefit when compared with cytotoxic chemotherapy, with an absolute reduction in the risk of progression of 22% - 30% as well as an advantage achieved in terms of ORR [36].

As a matter of fact, the results of the recent meta-analysis [36] indicated the significant role of attrition in the observed magnitude of benefit of a "targeted" treatment strategy that as the rate of patients analyzed or positive for sensitizing EGFR mutation increases (and thus the attrition rate decreases), the HR in favor of the EGFR-TKI decreases. When the attrition is relatively low (e.g. the Asian "clinically enriched" population of the two retrospective front-line trials [27,28], a non-molecular selection strategy may still be able to detect some degree of benefit for EGFR-TKI in the target population. Conversely, when the attrition bias is high (e.g. in mostly Caucasian patient populations where the rate of EGFR mutations is expected to be <10%), not only may a po-

tential benefit for EGFR-M+ patients be easily missed using a non selection strategy but we can also incur in the risk of exposing patients to a significantly detrimental effect, as observed in the Tarceva OR CHemotherapy trial [37], comparing erlotinib with standard chemotherapy as front-line treatment of unselected, advanced NSCLC patients [36].

Concerning toxicity, gefitinib appears to be well tolerated when administered as first-line treatment of patients with advanced NSCLC. Notably, in the IPASS trial [27], gefitinib was associated with a lower rate of severe adverse events (defined as grade 3 or 4 according to the Common Terminology Criteria for Adverse Events, 28.7% vs 61.0% for gefitinib and chemotherapy, respectively).

Differing substantially from toxicity reported, gefitinib was associated with better tolerance in all randomized trials comparing first-line gefitinib to platinum-based chemotherapy [27-30]. Although the most common adverse events in patients receiving gefitinib were cutaneous toxicity (skin rash, dry skin), diarrhea and liver dysfunction usually consisting in asymptomatic hypertransaminasemia, patients assigned to gefitinib arm suffered significantly less hematological toxicity, emesis, fatigue, neurotoxicity, constipation and hair loss, compared to patients treated with platinum-based chemotherapy. In particular, as reviewed recently [2], lower rate of severe adverse events (defined as grade 3 or 4 according to the Common Terminology Criteria for Adverse Events, 28.7% vs 61.0% for gefitinib and chemotherapy, respectively, a lower rate of adverse events leading to discontinuation of the drug (6.9% vs 13.6%) and a lower rate of dose modification due to toxic effects (16.1% for gefitinib vs 35.2% for carboplatin and 37.5% for paclitaxel) were reported in IPASS trial [27]. Likewise, in the NEJ002 trial [32], gefitinib confirmed a significantly lower incidence of severe toxic effects compared to carboplatin plus paclitaxel (41.2% vs 71.7%, p < 0.001).

Among potentially life-threatening events described with the use of gefitinib, interstitial lung disease (ILD) was relatively uncommon. As described recently [2], it was identified in 16 patients (2.6%) in the IPASS trial [27], 2 patients (2.3%) in the WJTOG3405 trial [29], 6 patients (5.3%) in the NEJ002 trial [30]. Five of these 24 cases were lethal, and further 2 lethal cases of ILD were described in the 159 patients treated with gefitinib in the First-SIGNAL trial [28], leading to a total of 7 lethal ILD toxicities in the 967 patients overall evaluated in the 4 trials (0.7%).

In this regard, identification of sensitizing EGFR mutations as the preferential molecular target of EGFR-TKI was reported to be crucial to get impressive benefit achieved with EGFR-TKI over classical cytotoxic che-

motherapy if compared with the benefit of chemotherapy versus best supportive care in the same setting [38,39]. Importantly, this benefit was not gained at the expense of an increased toxicity rate; hematological toxic effects were significantly decreased in patients receiving gefitinib, thus further increasing the therapeutic index of such a targeted approach. When a composite measurement of both efficacy and toxicity is used, an EGFR M+ patient was reported to be at least 67 times more likely to derive clinical benefit than to be harmed by upfront treatment with an EGFR-TKI rather than chemotherapy [36].

Whilst representing the strongest endpoint for clinical research in oncology, none of these randomized trials demonstrated a statistically significant improvement with gefitinib in terms of OS. Indeed, differences in OS were reported to be potentially conditioned by cross-over, and a relevant number of patients assigned to chemotherapy arm received an EGFR tyrosine kinase inhibitor (gefitinib or erlotinib) as second or third-line treatment after disease progression [2]. As the number of trials is small (n = 3), the limitations of the trials with respect to patient populations (all patients are from Asia) are important. How this may or may not impact generalization to Western countries is not clear. Moreover, in a series of Western patients with EGFR mutation positive NSCLC, treated with erlotinib, similar OS was reported for patients receiving the EGFR tyrosine kinase inhibitor as first-line or as second-line (median OS was 28.0 months and 27.0 months, respectively) [40].

5. Conclusion

In patients with advanced NSCLC selected for the presence of EGFR mutation, the administration of first-line gefitinib, compared to standard platinum-based chemotherapy, is associated with longer PFS, higher ORR. The current meta-analysis does not provide any data on better tolerability of gefitinib compared to chemotherapy because of different toxicity observed between two treatment modalities. Since no data on EGFR M-negative patients has been included in the meta-analysis the conclusion on the importance of EGFR mutation testing in order to plan first-line therapy cannot be drawn from the presented work, even though it is correct. Accordingly, the HR and also OR for the ORR obtained within this meta-analysis supports the efficacy of gefitinib strongly, and as a superior medical evidence that may help to draw the attention of the physicians and the health authority, stresses on the importance of the identification of EGFR mutation test as well as gefitinib use in routine practice of NSCLC which is characterized by significant heterogeneity, premonitory for the likelihood of deriving substantial therapeutic benefit.

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