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REVIEW ARTICLE

First-line Systemic Therapy for Metastatic Non-small-cell Lung Cancer — A Review

Yuh-Min Chen [1,2]*, Jacqueline Whang-Peng [2,3], Chien-Ming Chen [2,3]

[1] Chest Department, Taipei Veterans General Hospital, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[2] Center of Excellence in Cancer Research, School of Medicine, Taipei Medical University, Taipei, Taiwan
[3] Division of Cancer Center, Shaun-Ho Hospital, Taipei Medical University, Taipei, Taiwan

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Our aim was to review and update the current status of systemic therapy for metastatic non-small-cell lung cancer (NSCLC). We reviewed Phase II or Phase III clinical trials of first-line third-generation chemotherapy regimens (docetaxel, gemcitabine, paclitaxel, pemetrexed, and vinorelbine) and targeted agents (bevacizumab, cetuximab, erlotinib, and gefitinib) identified through Medline, international conferences, and websites of related organizations. We found effort should be taken to find out whether patients have a tumor epidermal growth factor receptor (EGFR)-active mutation. EGFR-tyrosine kinase inhibitor could be given as first-line treatment for patients with active EGFR mutations (Exon 19 deletions and Exon 21 L858R), whereas patients with a good performance status and wild-type or unknown EGFR mutation status should be treated with platinum-based doublets (platinum plus a third-generation chemotherapy agent). No specific third-generation agent is clearly superior for use in combination with a platinum agent. However, pemetrexed is more active in nonsquamous NSCLC. The survival advantage of platinum-based doublets over non-platinum combinations or older combinations is modest. Systemic chemotherapy beyond four to six cycles impedes quality of life without prolonging life. However, data suggest switching to maintenance with pemetrexed or erlotinib therapy is effective in prolonging patient survival. The addition of bevacizumab to carboplatin and paclitaxel has shown improved survival, and a large-scale Phase IV study showed the efficacy and safety of the combination of bevacizumab with platinum-based doublets. In conclusion, in tumor EGFR-mutated NSCLC, EGFR-tyrosine kinase inhibitor is the first-line treatment of choice for patients with metastatic disease. The combination of a platinum agent plus a third-generation agent continues to be the standard of care for those patients with tumor EGFR wild-type or unknown status. Pemetrexed is more active in patients with non-squamous NSCLC, and bevacizumab in combination with platinum-based doublets can also be considered in patients with non-squamous NSCLC. As differences between the regimens are small, a detailed discussion with the patient regarding treatment toxicity and patient preference will help in making the regimen choice.

1. Introduction

Lung cancer is the leading cause of cancer death in the world and non-small-cell lung cancer (NSCLC) accounts for the majority of lung cancer cases.[1,2] Adenocarcinoma and squamous cell carcinoma (SCC) are two major histologic subtypes of NSCLC. The incidence of adenocarcinoma has increased in recent decades, whereas the incidence of SCC has reached a plateau or has decreased, mainly because of changes in smoking behavior with the use of filtered cigarettes with low tar, low nicotine, and increased nitrate levels.[3,4] Most NSCLC patients face the option of systemic chemotherapy or targeted therapy. Because more than 40% of NSCLC patients present with metastatic disease, they are suggested to receive systemic therapy, and the majority of patients with Stage I–III tumors treated with curative intent eventually develop recurrence.[5]

Third-generation anti-cancer drugs and their combination with platinum have shown better response rates and survival than the conventional regimens during the last decade.[6–8] Pemetrexed, a recently available third-generation chemotherapeutic agent, was found to be more effective in non-squamous NSCLC.[9,10] Furthermore, bevacizumab, a monoclonal antibody of vascular endothelial growth factor, was found to enhance chemotherapy efficacy against non-squamous NSCLC.[11]

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), such as erlotinib and gefitinib, are a new class of anti-cancer agents that have been used for nearly one decade.[6] It was found that adenocarcinoma had a better response to this class

* Corresponding author. Chest Department, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Rd, Taipei 112, Taiwan.
E-mail: Y.-M. Chen <ymchen@vghtpe.gov.tw>

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of targeted agent, whereas other subtypes of NSCLC had a less satisfactory response because of the differing frequencies of tumor epidermal growth factor receptor (EGFR) mutations.[12] Recent clinical trials have also shown the high efficacy of EGFR-TKIs as first-line treatment for EGFR-mutated NSCLC, compared with platinum-based doublets, in terms of prolongation of progression-free survival (PFS) and less toxicity.[13–15] Together with the above findings, patients with adenocarcinoma have had better treatment options available and improved survival in recent years.[9,16]

In the present review, we briefly summarize the important studies performed in recent years, review guidelines, and analyze the feasibility of current therapy options for patients with NSCLC.

2. Systemic Chemotherapy

2.1. Platinum-based doublet chemotherapy

An updated review by a committee of the American Society of Clinical Oncology provides evidence supporting the use of chemotherapy in Stage IV NSCLC patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1, and possibly 2.[6] Clinical trials have supported the use of two chemotherapy agents rather than one, in terms of response rates and survival, although toxicity is increased.[17] No one specific platinum-based doublet containing a third-generation anti-cancer agent had better efficacy than the others, before the data of pemetrexed trials was available.[10,18–20] Drugs that may be combined with platinum include the third-generation cytotoxic drugs docetaxel, gemcitabine, paclitaxel, pemetrexed, and vinorelbine. Patients' quality of life is usually improved with chemotherapy, with improvements in disease-specific symptoms at a cost of some degree of worsening in drug-induced toxicities or symptoms.[21] Assessments of several regimens of chemotherapy also have shown that chemotherapy against NSCLC is cost effective.[22] In spite of these treatment benefits, it should be noted that the patients studied in most Phase II and Phase III chemotherapy clinical trials had a good PS, typically ECOG PS 0–1, and only a few PS 2 patients were enrolled. In addition, many studies restricted eligibility to patients more than 70 years old.

2.2. Cisplatin, carboplatin, or non-platinum-based chemotherapy

Platinum combinations are preferred over non-platinum combinations because they are superior in response rate and result in a marginally/insignificantly longer overall survival.[6] The choice of either cisplatin or carboplatin is acceptable. However, carboplatin is not reimbursed in Taiwan except for patients with impaired renal function. Cisplatin is slightly more effective than carboplatin, but also has more adverse effects. Cisplatin combinations have a higher response rate than carboplatin and may improve survival when combined with third-generation agents.[6,23,24] Carboplatin is less likely to cause nausea, vomiting, neurotoxicity, and nephrotoxicity than cisplatin, but is more likely to cause myelosuppression, especially thrombocytopenia. Non-platinum therapy combinations are reasonable in patients who have contraindications to the use of platinum therapy, such as pre-existing heart failure, renal insufficiency or failure, neuropathy, or hearing impairment. Triplet chemotherapy showed no survival benefit, but had significantly higher toxicities.[17,19]

2.3. Treatment cycles

How many cycles of first-line chemotherapy should be given? It is generally accepted that first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in stage IV NSCLC patients whose disease is not responding to treatment.[6] Cytotoxic doublet chemotherapy should be administered for no more than six cycles, even in those patients who have responded to treatment. For patients who have stable disease or who respond to first-line chemotherapy, the present evidence does not support the continuation of doublet chemotherapy beyond six cycles.[6,25,26]

2.4. Maintenance therapy

With the advent of effective second-line cytotoxic drugs that improve survival for NSCLC patients who have progressive disease after first-line chemotherapy, there is a renewed interest in whether initiation of a different or non-cross-resistant drug immediately after completion of first-line chemotherapy, or the initiation of a different chemotherapy before disease progression, will improve survival.[27–30] In general, most studies showed improvement in PFS, but not overall survival, either by continuing an effective chemotherapy beyond four cycles or by immediately initiating alternative chemotherapy.[27–30] However, the improvement in PFS is tempered by an increase in adverse effects from additional cytotoxic chemotherapy. Of the many chemotherapeutic agents, including gemcitabine, vinorelbine, docetaxel, and pemetrexed, used in maintenance therapy, only pemetrexed was approved by the Food and Drug Administration on 2 July 2010 for maintenance therapy in NSCLC patients with advanced disease. Pemetrexed maintenance therapy has demonstrated a significant survival benefit compared with the best supportive care after first-line chemotherapy.[28]

Another type of maintenance therapy after first-line chemotherapy is the use of EGFR-TKIs.[31] Median PFS was longer with erlotinib maintenance therapy than with placebo treatment [2.9 months *vs.* 2.6 months, hazards ratio (HR) 0.71, 95% confidence interval 0.62–0.82; $p < 0.0001$] and overall survival was prolonged with erlotinib maintenance treatment versus placebo treatment (median 12 months *vs.* 11 months, HR 0.81, 95% confidence interval 0.7–0.95, $p = 0.0088$) in a large Phase III randomized trial.

2.5. Chemotherapy with targeted therapy

Chemotherapy in combination with targeted therapy has been used for a decade already, although chemotherapy combined with small molecular tyrosine kinase inhibitors has generally failed.[32–35] However, a small study showed promise with preliminary efficacy when chemotherapy was combined with intercalated EGFR-TKIs.[36] A Phase III randomized study is ongoing to verify this treatment strategy. Chemotherapy in combination with EGFR monoclonal antibody has also been studied in Phase II and Phase III trials, and only the FLEX study showed a significant 1.2-month survival prolongation when adding cetuximab to vinorelbine plus cisplatin chemotherapy.[37] Cetuximab is suggested for use in combination with vinorelbine plus cisplatin as one of the treatment choices in treatment-naïve advanced NSCLC patients with clinical characteristics similar to those in the FLEX study in the USA,[6] but not in Europe at present, because of the lack of a predictor of who will respond well to this combination of treatment. However, a recently published retrospective analysis of the correlation of first-cycle skin rash with treatment response in the FLEX study showed first-cycle skin rash was associated with a better outcome. First-cycle skin rash might be a surrogate clinical marker that could be used to tailor cetuximab treatment for advanced NSCLC in those patients who would be most likely to derive a significant benefit.[38] With regard to anti-angiogenesis targeted therapy, only bevacizumab (monoclonal antibody

of vascular endothelial growth factor) was approved for use in first-line NSCLC treatment in combination with pacliaxel plus carboplatin.[6,11] The recommended dose is 15 mg/kg every 3 weeks in combination with paclitaxel and carboplatin in non-squamous NSCLC patients with a PS of 0 or 1, and without brain metastases Bevacizumab may be continued until disease progression. This recommendation is based on a Phase III randomized trial (ECOG4599) involving 878 non-squamous NSCLC patients. The study showed there was a two-month improvement in overall survival when bevacizumab was added to a paclitaxel plus carboplatin regimen (12.3 months *vs.* 10.3 months; HR = 0.79, $p = 0.003$).[11] The chemotherapy regimen was confined to paclitaxel plus carboplatin only because another Phase III randomized trial of bevacizumab in combination with gemcitabine and cisplatin showed an improvement in response rate and modest PFS improvement, but not overall survival.[39] However, a recently published Phase IV study of bevacizumab in combination with platinum-based chemotherapy (SAiL) documented its safety and efficacy, with a median survival of 12.3 months for NSCLC patients and 14.6 months for patients with adenocarcinoma.[40] The disease control rate was 88%, and median survival was high up to 18.9 months for Asian patients with adenocarcinoma. Thus, it seems there is no need to confine bevacizumab treatment to use with paclitaxel plus carboplatin only. Patients with SCC are not suggested to receive bevacizumab-containing chemotherapy because of the risk of massive hemoptysis.[41,42]

2.6. Histologic subtype and choice of chemotherapeutic agent

It is true that the histologic subtype of NSCLC affects the choice of first-line chemotherapy regimen. Three large Phase III randomized trials involving pemetrexed (second-line docetaxel *vs.* pemetrexed; first-line gemcitabine + cisplatin *vs.* pemetrexed + cisplatin; pemetrexed maintenance therapy *vs.* best supportive care)[20,28,43] showed pemetrexed had better efficacy, including PFS and overall survival, in patients with non-squamous cell carcinoma than in those with SCC (Table 1).[10]

3. EGFR-TKI

3.1. First-line EGFR-TKI treatment in tumor EGFR-mutated NSCLC patients

EGFR-TKIs, such as erlotinib and gefitinib, are a new class of anticancer agents that have been used for nearly a decade.[6] It was found that the tumor EGFR mutations that occur mainly in adenocarcinoma, especially tumor EGFR exon 19 deletions and exon 21 L858R mutations (activating mutations), predicted a better response to this class of targeted agents.[12,44] In clinically or molecularly unselected NSCLC patients, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line therapy,[32–35] and in clinically or molecularly unselected patients, evidence is insufficient to recommend single-agent erlotinib or gefitinib as first-line therapy. In contrast, recent Phase III randomized clinical trials showed the high efficacy of EGFR-TKIs as first-line treatment for EGFR-mutated NSCLC, compared with platinum-based doublets, in terms of prolongation of PFS, better quality of life, and fewer treatment-induced toxicities (Table 2).[13–15,45] Thus, first-line treatment with erlotinib or gefitinib may be recommended for patients with activating EGFR mutations. If the EGFR mutation status is negative or unknown, then cytotoxic chemotherapy is preferred.

3.2. Erlotinib or gefitinib

Both agents are highly active in those patients whose tumors had activating mutations, such as exon 19 deletions or exon 21 L858R mutations.[46,47] Thus, both agents can be used in first-line treatment of patients whose tumors have EGFR activating mutations. However, the side effects of EGFR-TKIs, such as skin rashes and a nausea sensation, are relatively more frequent or severe in patients who receive erlotinib than in those taking gefitinib. The occurrence of other side effects, such as diarrhea, was similar between the two agents, or even slightly less frequent, such as pneumonitis, with erlotinib treatment. It is also recommended that patients with central nervous system metastases or meningeal carcinomatosis be treated with erlotinib instead of gefitinib, because of the higher blood-brain-barrier penetration rate and higher cerebrospinal fluid concentrations of erlotinib and its active metabolites than with gefitinib.[48–51]

3.3. Second-generation TKI

Second-generation TKI or multi-targeted agents, such as afatinib (BIBW-2992) and vandetanib, are still in clinical trials and not available for routine clinical use at present.[52,53] In general, these agents can be used alone or in combination with other targeted agents if the agent belongs to the EGFR-TKI family; and they are usually used in combination with chemotherapy when they are anti-angiogenetic agents.

Table 1 Response rate, progression-free survival, and overall survival by histologic subtype in three pemetrexed studies

Histologic subtype	Second-line pemetrexed versus docetaxel ($n = 571$)		First-line pemetrexed + cisplatin versus gemcitabine + cisplatin ($n = 1725$)		Maintenance pemetrexed versus placebo ($n = 663$)	
	Pemetrexed	Docetaxel	Pemetrexed	Gemcitabine	Pemetrexed	Placebo
Squamous cell carcinoma (n)	78	94	244	229	116	66
Response rate (%)	2.8	8.1	23.4	31.4	3.1	1.8
Median PFS (mo)	2.3	2.7	4.4	5.5	2.4	2.5
HR (95% CI)	1.40 (1.01–1.96)		1.36 (1.12–1.65)		1.03 (0.71–1.49)	
Median survival (mo)	6.2	7.4	9.4	10.8	9.9	10.8
HR (95% CI)	1.56 (1.08–2.26)		1.23 (1.00–1.51)		1.07 (0.77–1.50)	
Non-squamous NSCLC	205	194	618	634	325	156
Response rate (%)	11.5	9.0	28.6	22.2	3.4	0
Median PFS (mo)	3.1	3.0	5.3	5.0	4.4	1.8
HR (95% CI)	0.82 (0.66–1.02)		0.95 (0.84–1.06)		0.47 (0.37–0.60)	
Median survival (mo)	9.3	8.0	11.0	10.1	15.5	10.3
HR (95% CI)	0.78 (0.61–1.00)		0.84 (0.74–0.96)		0.70 (0.56–0.88)	

CI = confidence interval; HR = hazards ratio; NSCLC = non-small-cell lung cancer; PFS = progression-free survival.

Table 2 Four phase III randomized trials comparing first-line epidermal growth factor receptor-tyrosine kinase inhibitors and chemotherapy treatment in clinically or molecularly selected non-small-cell lung cancer patients

	I-PASS		NEJSG		WJTOG3405		OPTIMAL (CTONG 0802)	
	Gefitinib	Paclitaxel + carboplatin ($^{\#}p$)	Gefitinib	Paclitaxel + carboplatin ($^{\#}p$)	Gefitinib	Docetaxel + cislatin ($^{\#}p$)	Erlotinib	Gemcitabine + carboplatin ($^{\#}p$)
EGFR active mutation* (n)	132	129	114	110	88	89	82	72
Response rate (%)	71.2	47.3 (<0.001)	73.7	30.7 (<0.001)	62.1	32.2 (<0.0001)	83	36 (<0.001)
Progression-free survival, mo	9.5	4.9 (<0.001)	10.8	5.4 (<0.001)	9.2	6.3 (<0.0001)	13.1	4.6 (<0.001)
Overall survival, mo	21.6	21.9 (0.99)	30.5	23.6 (0.31)	UA	UA	UA	UA

$^{\#}p$ value when comparing epidermal growth factor receptor-tyrosine kinase inhibitors group.
EGFR = epidermal growth factor receptor; UA = unavailable.
* Exon 19 deletions or L858R.

4. Conclusions

In NSCLC patients with a tumor-active EGFR mutation and metastatic disease, EGFR-TKI is the first-line treatment of choice. The combination of a platinum agent with a third-generation agent continues to be the standard of care for those patients with tumor EGFR of a wild-type or unknown status. Pemetrexed is more active in patients with non-squamous NSCLC, and bevacizumab in combination with platinum-based doublets can also be considered in non-squamous NSCLC.

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