A Review of Treatment in Non-small-cell Lung Cancer

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Abstract

Non-small-cell lung cancer (NSCLC) accounts for approximately 85 % of all lung cancer cases. For patients with early-stage disease, surgery followed by adjuvant chemotherapy is the optimal treatment. For patients with locally advanced disease, the standard approach is chemoradiotherapy, since it offers a small but statistically significant prolongation in survival compared with the sequential approach. It should be noted, however, that this approach is associated with significant toxicity and it only applies to patients with good performance status. For patients with metastatic disease, chemotherapy represents the cornerstone of treatment and results in a median survival of approximately 10 months. Recently, the addition of bevacizumab or cetuximab to chemotherapy doublets and the use of gefitinib and erlotinib has improved the outcome in selected patients with advanced NSCLC. Hopefully, advances in understanding the molecular biology of cancer and mechanisms of tumourigenesis will facilitate the discovery and development of novel 'targeted agents' and will further improve outcomes for these patients.

Keywords

Lung carcinoma, non-small-cell lung cancer (NSCLC), adjuvant, chemotherapy, targeted agents, erlotinib, maintenance treatment, gefitinib, bevacizumab

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The term lung cancer refers to carcinomas that originate from the respiratory epithelium. Approximately 85 % of all lung cancers are classified as non-small-cell lung cancer (NSCLC), 10 % are small cell lung cancer and other histological variants account for about 5 %.[1] Lung cancer represents the second most common type of cancer in both men (after prostate cancer) and women (after breast cancer) in the Western world.[1] It is estimated that approximately 220,000 new cases of lung cancer occurred during 2009 in the US.[1,2] Both the absolute and relative frequency of lung cancer has risen dramatically, for example the age-adjusted death rates from lung cancer were similar to that of pancreatic cancer prior to 1930 for men and prior to 1960 for women.[1] Although the incidence of lung cancer is declining in men, it continues to rise in women.[1] Unfortunately, lung cancer remains by far the most frequent cause of cancer-related death, with approximately 159,000 deaths observed in 2009 in the US.[1] By contrast, colorectal, breast and prostate cancers combined will have been responsible for only 118,000 deaths.[1] Although lung cancer deaths have begun to decline in men, the death rate in women continues to rise and almost half of all lung cancer deaths now occur in women.[1] The vast majority of patients are diagnosed with advanced, unresectable disease that remains incurable. This has a five-year survival rate of <5 %,[3] whereas the five-year survival rate for all stages is approximately 15 %.[4]

Data linking cigarette smoking to human lung cancer include a huge bank of both prospective and retrospective epidemiological research first reported in 1950.[5–7] A heavy smoker is considered to have a cumulative lung cancer risk as high as 30 % compared with a lifetime risk of lung cancer of ≤1 % in people who have never smoked.[8] The relative risk of lung cancer development in a long-term smoker compared with someone who has never smoked is estimated to be 10- to 30-fold greater.[8] The relative risk increases with both the number of cigarettes smoked per day as well as the lifetime duration of smoking. Smoking cessation clearly decreases the risk of lung cancer among former smokers compared with current smokers.[9] The reduction in risk becomes evident within five years of becoming abstinent and it has been estimated that former smokers who have been abstinent for >15 years have an 80–90 % reduction in risk of lung cancer compared with current smokers.[8] Environmental tobacco smoke (i.e. passive or 'second-hand' exposure) is associated with an increase in the risk of lung cancer, although this increase is far lower than that observed with active smoking.[10,11] The purpose of this article is to present current data regarding the treatment of NSCLC.

Early-stage Disease

Surgery

Surgery is the cornerstone of management for patients with early-stage (I–II) NSCLC and selected patients with stage IIIA disease (T3N1).[12] The Lung Cancer Study Group concluded that lobectomy is a superior operation for T1N0 NSCLC, based on a randomised trial of lobectomy versus more limited resection.[13] Thus, in patients with stage I and II NSCLC who are medically fit for conventional surgical resection, lobectomy or greater resection are recommended rather than sublobar resections (wedge or segmentectomy).[12] In patients who for medical reasons (severely compromised pulmonary function, advanced age or other extensive comorbidity) cannot tolerate a full lobectomy, a more limited operation (sublobar) is recommended.[14] For patients with more advanced tumours in whom complete tumour resection cannot

Table 1: Phase III Trials of Bevacizumab plus Chemotherapy Doublets as First-line Treatment of Non-small-cell Lung Cancer

Study	n	Treatment	TTP	p value	OS (Months)	p value
ECOG 4599[49]	878	PCL/carboplatin	6.2	<0.001	10.3	0.003
		± bevacizumab	4.5		12.3	
AVAiL[48]	1,043	GMB/CDDP	6.1	0.003	13.1	NS
		± bevacizumab	6.7	0.03	13.6	
		7.5 mg/kg	6.5		13.4	
		15 mg/kg				

AVAiL = Avastin in lung; CDDP = cisplatin; ECOG = Eastern Cooperative Oncology Group; GMB = gemcitabine; NS = non-significant; OS = overall survival; PCL = paclitaxel; TTP = time to tumour progression.

Table 2: Cetuximab in Combination with Chemotherapy as First-line Treatment in Non-small-cell Lung Cancer

Trial	n	Treatment	OS (Months)	p value
FLEX study[54]	1,125	CDDP/VNB ± cetuximab	11.3 versus 10.1	0.044
BMS 099[55]	676	Carboplatin/taxane ± cetuximab	PFS: 4.4 versus 4.24	0.236

CDDP = cisplatin; FLEX = cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; taxane = either paclitaxel or docetaxel; VNB = vinorelbine.

be achieved with lobectomy, sleeve lobectomy is recommended over pneumonectomy because it preserves pulmonary function.[12]

Definitive Radiotherapy

Although surgery is the treatment of choice for NSCLC patients with early-stage disease, some never undergo surgery. Common reasons for not undergoing surgery are older age, the presence of serious co-morbidities and patient refusal. For those patients who do not undergo an operation, radiotherapy can be administered with curative intent, albeit with lower survival rates when compared to surgery.[15,16]

Adjuvant Chemotherapy

Recent data from randomised adjuvant clinical trials[17,18] and a recent meta-analysis[19] have changed the standard of care for patients with completely resected NSCLC. The survival benefit observed with adjuvant chemotherapy was confirmed by a meta-analysis of five randomised trials[17,18,20–22] with 4,584 patients registered in the Lung Adjuvant Cisplatin Evaluation database.[19] This meta-analysis demonstrated a 5.4 % increase in five-year survival in favour of adjuvant chemotherapy compared with observation (hazard ratio [HR]: 0.89; 95 % confidence interval [CI] 0.82–0.96).[19] The survival benefit varied according to stage and was most pronounced for patients with stage II and IIIA disease. The improvement in survival in patients with stage IB disease did not reach statistical significance. Patients with stage IA disease appeared to do worse with adjuvant chemotherapy. Some retrospective data suggest that patients with stage IB disease and tumours ≥4 cm may also benefit from adjuvant chemotherapy.[23] A more recent meta-analysis based on individual patient data confirmed the survival benefit in favour of adjuvant chemotherapy.[24] This benefit was irrespective of whether chemotherapy was adjuvant to surgery alone or adjuvant to surgery plus radiotherapy.

Adjuvant Radiotherapy after Surgical Resection

The post-operative radiotherapy (PORT) meta-analysis,[25,26] which included 2,128 patients, demonstrated that the use of post-operative radiotherapy was associated with a detrimental effect on survival, which was more pronounced for patients with lower nodal status. The PORT meta-analysis has been criticised, however, for its long enrolment period and use of different types of machines, techniques and doses.

Three randomised phase III trials published subsequent to the PORT meta-analysis failed to support a benefit for the use of post-operative radiotherapy.[27–29] For patients with N2-positive disease, however, a retrospective analysis demonstrated higher survival for those patients who had received post-operative radiotherapy.[18] On the basis of these results, routine post-operative radiotherapy is not recommended for patients with completely resected stage I–IIIA NSCLC.[30,31]

Locally Advanced Disease

Up to one-third of patients with NSCLC present with disease that remains local to the thorax but is considered too extensive for surgical treatment (stages IIIA and IIIB). Concurrent chemoradiotherapy is considered the standard therapy for unresectable stage III NSCLC.[32] The concurrent administration of chemotherapy plus radiotherapy results in a modest but statistically significant survival benefit compared with sequential administration, as demonstrated by randomised phase III trials.[33,34] This approach is, however, associated with significant toxicity and it only applies to patients with good performance status.[35] The role of surgery in the subcategory of patients with N2 disease was tested in two randomised phase III trials. A European trial treated patients with histologically proven N2 disease with three cycles of cisplatin-based chemotherapy, then allocated them to surgery or sequential thoracic radiotherapy. After a median 72-month follow-up, there was no significant difference in overall survival (OS) or progression-free survival (PFS).[36] An American trial randomised patients with N2 disease to either chemotherapy (two cycles of cisplatin/etoposide) and concurrent 45Gy radiotherapy followed by surgery (with two cycles of post-operative chemotherapy) versus two cycles of cisplatin/etoposide and 61Gy radiotherapy.[37] This trial demonstrated a PFS benefit in favour of the surgical arm, but no difference in OS was observed. Additionally, surgery was associated with higher toxicity.

Metastatic Disease

Chemotherapy remains the cornerstone of treatment for patients with stage IV disease. An individual patient data meta-analysis that included 16 randomised phase III trials and 2,714 patients has demonstrated that chemotherapy offers an OS benefit with an absolute improvement in survival of 9 % at 12 months compared with best supportive care.[38] Chemotherapy doublets are superior to a

Table 3: Phase III Trials of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors versus Chemotherapy as First-line Treatment in Non-small-cell Lung Cancer

Study	n	Treatment	PFS	p value	OS (Months)	p value
IPASS[61] EGFR mutated	261	Gefitinib versus paclitaxel/carboplatin	HR for progression, 0.48, 95% CI 0.36–0.64	<0.001	NR	
WJTOG3405*[62]	177	Gefitinib versus cisplatin/docetaxel	9.2 months 6.3 months	<0.0001	NR	
NEJ002*[63]	230	Gefitinib versus paclitaxel/carboplatin	10.4 months 5.5 months	<0.001	30.5 23.6	NS
CTONG 0802*[64]	154	Erlotinib versus gemcitabine/carboplatin	13.1 months 4.6 months	<0.0001	NR	

**Only patients with epidermal growth factor receptor (EGFR)-mutated tumours. CI = confidence interval; HR = hazard ratio; IPASS = Iressa Pan-Asia Study; NA = not applicable; NR = not reported; NS = non-significant; OS = overall survival; PFS = progression-free survival; WJTOG = West Japan Thoracic Oncology Group.*

single agent in first-line treatment[39,40] and three-drug combinations do not offer any benefit in terms of OS compared with two-drug regimens.[40] The American Society of Clinical Oncology recommends cisplatin-based doublets because they are associated with a marginal one-year survival benefit compared with platinum-free regimens.[41] Platinum-free regimens represent an alternative in patients who cannot tolerate platinum-based treatment. Direct comparison of several doublets in randomised phase III trials has failed to demonstrate that one doublet is clearly superior to another.[42] Thus no particular regimen can be recommended as the 'gold standard'.[43] A very interesting Phase III trial was recently published by Scagliotti et al.[44] This was the first trial clearly demonstrating a significant interaction between treatment efficacy and tumour histology. This non-inferiority, Phase III trial randomised 1,725 chemotherapy-naïve patients with stage IIIB/IV NSCLC to cisplatin/gemcitabine or cisplatin/pemetrexed. OS for cisplatin/pemetrexed was non-inferior to cisplatin/gemcitabine (median survival 10.3 versus 10.3 months, respectively, HR 0.94, 95 % CI 0.84–1.05) in the whole cohort of patients. OS was, however, statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (n=847, 12.6 versus 10.9 months, respectively) and large-cell carcinoma histology (n=153, 10.4 versus 6.7 months, respectively). In patients with squamous cell histology, there was a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed (n=473; 10.8 versus 9.4 months, respectively).

Targeted Therapies in First-line Treatment

Bevacizumab

Angiogenesis, the formation of new blood vessels, is a fundamental process for the development of solid tumours and the growth of secondary metastatic lesions.[45] Vascular endothelial growth factor (VEGF) acts to promote normal and tumour angiogenesis.[46] Bevacizumab is a recombinant, humanised, monoclonal antibody against VEGF.[47] Two Phase III trials have evaluated the role of bevacizumab in combination with chemotherapy as first-line treatment (see *Table 1*). Bevacizumab when added to chemotherapy doublets offers a clinical benefit in terms of PFS (Avastin in lung [AVAiL] study and Eastern Cooperative Oncology Group [ECOG] 4599 study)[48,49] and OS (ECOG 4599).[49] The AVAiL trial did not demonstrate an OS benefit, but it should be underlined that its primary end-point was PFS and the study was not powered to demonstrate an OS difference. In these trials bevacizumab was continued until disease progression. Two large Phase IV studies (the Safety of avastin in lung cancer study[50] and the Aerosol Research and Inhalation Epidemiology Study[51]) have confirmed that bevacizumab is safe and feasible in combination with chemotherapy in first-line NSCLC treatment. The optimal dose of bevacizumab has not been determined since the ECOG4599 trial[49] used a dose of 15 mg/kg while the European AVAiL trial[48] yielded positive results for both doses tested (7.5 and 15 mg/kg). It should be noted that due to the significant risk of haemorrhage, a number of patients were excluded from bevacizumab trials. These patients had:

- squamous histology;
- history of haemoptysis (more than half a teaspoon of bright red blood per event);
- central nervous system metastases;
- history of thrombotic or haemorrhagic disorders;
- therapeutic anticoagulation;
- patients with tumours invading or abutting major blood vessels;
- clinically significant cardiovascular disease; or
- medically uncontrolled hypertension.

Thus, bevacizumab is recommended in combination with chemotherapy as first-line treatment in patients with certain clinical characteristics.

Cetuximab

Epidermal growth factor receptor (EGFR) is a transmembrane receptor that is highly expressed in NSCLC.[52] Binding of ligands (epidermal growth factor, tumour growth factor-alpha, betacellulin, epiregulin and amphiregullin) to the extracellular EGFR domain results in autophosphorylation through tyrosine kinase activity.[53] This initiates an intracellular signal transduction cascade that affects cell proliferation, motility and survival.[52] Monoclonal antibodies compete with ligands to bind with the extracellular part of the EGFR. When ligand and EGFR interaction is inhibited, the EGFR dependent on the downstream pathway cannot be triggered (when not permanently activated by a mutation event). Two prospective, randomised Phase III trials evaluated the combination of cetuximab and chemotherapy doublets (see *Table 2*). The first compared a cisplatin/vinorelbine plus or minus cetuximab in 1,125 chemo-naïve NSCLC patients with EGFR immunohistochemistry-positive tumours. Although PFS was identical between the two arms (4.8 versus 4.8 months), the cetuximab arm had a modest, although statistically significant, OS prolongation (11.3 versus 10.1 months; p=0.044).[54] A second Phase III trial investigating carboplatin plus a taxane (either paclitaxel or docetaxel) with or without cetuximab as first-line treatment for patients with metastatic NSCLC failed to show any improvement in PFS, the study's primary end-point (median PFS for carboplatin/taxane versus carboplatin/taxane/cetuximab was 4.2 versus 4.4 months, respectively; p=0.23).[55] On the basis of these results, cetuximab was not registered by the European Medicines Agency for first-line treatment and further studies are needed to elucidate its role in the treatment of NSCLC.

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Erlotinib and gefitinib are orally administered inhibitors of the tyrosine kinase domain of the intracellular part of EGFR.[47] Recently two groups have reported the identification of mutations of the tyrosine kinase coding domain (exons 18–21) of the *EGFR* gene.[56,57] The discovery of these mutations in tumours from NSCLC patients was immediately linked with response to gefitinib.[56,57] An association between the presence of these mutations and the efficacy of anti-EGFR tyrosine kinase inhibitor treatment has subsequently been reported, with several prospective Phase II clinical trials reporting response rates in the range of 70–90 % and a PFS of seven to 13 months.[58–60] The effects of single-agent gefitinib versus chemotherapy as first-line treatment of NSCLC has been tested in the context of three Phase III studies (see *Table 3*).[61–63]

The first of these trials, the Iressa Pan-Asia Study (IPASS), evaluated gefitinib in a cohort of clinically select patients – those of Asian ethnicity, with adenocarcinoma histology and never or light ex-smokers (<100 cigarettes in a lifetime). Gefitinib was compared to carboplatin/paclitaxel doublet as first-line treatment in 1,217 patients. This study demonstrated the superiority of gefitinib relative to the carboplatin/paclitaxel doublet in terms of PFS with a median PFS of gefitinib versus carboplatin/paclitaxel of 5.7 months versus 5.8 months and 12-month PFS of 25 versus 7 % (p <0.001).[61] There was a striking difference in PFS in patients with EGFR-mutated tumours treated with gefitinib compared with those treated with chemotherapy (9.5 versus 6.3 months; HR: 0.48; p<0.001). The predictive role of EGFR mutation was also demonstrated by the noteworthy differences in PFS observed in patients with EGFR-mutation-positive or -negative tumours when treated with gefitinib (9.5 versus 1.5 months). Two Japanese Phase III trials have evaluated gefitinib versus chemotherapy in patients selected on the basis of the EGFR mutation status of their tumour. These have confirmed the results of the IPASS study by demonstrating a provocative PFS benefit in favour of gefitinib. Gefitinib was associated with a more favourable toxicity profile in all trials. A similar trial of erlotinib versus the gemcitabine/carboplatin doublet in 154 Chinese NSCLC patients with EGFR-mutated tumours has been reported by Zhou et al.[64] This trial demonstrated a striking PFS difference in favour of erlotinib with a median PFS for erlotinib versus chemotherapy of 13.1 months versus 4.6 months, respectively (see *Table 3*). These data support the first-line use of EGFR tyrosine kinase inhibitors for patients with activating EGFR mutations. If EGFR mutation status is negative or unknown, then cytotoxic chemotherapy is preferred.[41]

Maintenance Treatment

Chemotherapy

Two Phase III trials have evaluated chemotherapeutic agents as maintenance treatment in patients who have not progressed after platinum-based first-line treatment. The first trial by Fidias et al., evaluated docetaxel[65] and the other trial by Ciuleanu et al., evaluated pemetrexed.[66] Both trials demonstrated a PFS benefit in favour of the maintenance arm[65,66] and one yielded an OS benefit.[66] It should be noted, however, that in the Fidias et al. trial, 95 % of patients in the immediate-therapy arm received docetaxel while only 63 % of patients in the delayed-therapy arm received docetaxel.[65] Similarly, only 19 % of the patients in the placebo arm had received pemetrexed as second-line treatment in the Ciuleanu et al. study.[66] Thus it is questionable whether survival benefit would have been maintained if cross-over was planned. In the Fidias trial,[65] when OS rates in patients that actually received intermediate and delayed docetaxel therapy were compared, the results were identical in both arms. Furthermore, it should also be noted that the trials only randomised patients who had not progressed after first-line treatment and thus only evaluated maintenance treatment in patients with known chemosensitive disease.

Targeted Agents

Erlotinib has been tested as maintenance treatment in the context of two Phase III trials.[67,68] The Sequential Tarceva in Unresectable NSCLC trial randomised 884 NSCLC patients who had not progressed after four cycles of platinum-based chemotherapy to receive erlotinib maintenance or placebo.[67] Erlotinib maintenance was associated with a modest but statistically significant prolongation of PFS, which was the primary end-point of the study. The median PFS of erlotinib versus placebo was 12.3 versus 11.1 weeks (HR 0.71, 95 % CI 0.62–0.82; p<0.0001). Furthermore, this trial demonstrated significantly longer survival in the erlotinib arm compared with the placebo arm (12 versus 11 months, HR 0.81; p=0.008). The Adjuvant tamoxifen longer against shorter (ATLAS) trial[68,69] was designed to evaluate the addition of erlotinib to bevacizumab maintenance in NSCLC patients who had not progressed after first-line treatment with platinum-based chemotherapy plus bevacizumab. This study met its primary end-point of demonstrating an OS benefit in favour of the combination, but no survival benefit was observed.[69] It should be noted, however, that this trial was not powered to detect a difference in OS.[68,69] Only pemetrexed has received approval as single-agent maintenance treatment in patients not progressing after first-line chemotherapy.

Second-line Treatment

Docetaxel has received approval as a second-line treatment on the basis of the results of a randomised Phase III trial that demonstrated a time-to-tumour-progression and an OS prolongation over placebo.[70] This study established docetaxel as the standard comparator arm for subsequent randomised trials. A more recent, non-inferiority Phase III study compared docetaxel with pemetrexed as second-line therapy in NSCLC.[71] No significant difference was observed in OS or one-year survival, while pemetrexed was associated with a more favourable toxicity profile. This trial led to the approval of pemeterexed for the second-line treatment of NSCLC.

Targeted Agents

Erlotinib has received approval by health authorities as second-line treatment for patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen on the basis of the results of BR-21, a Phase III trial by the National Cancer Institute of Canada.[72] Patients treated with erlotinib experienced significantly longer PFS and OS than those taking a placebo. Gefitinib was compared with docetaxel in the context of a Phase III, non-inferiority trial (INTEREST trial).[73] This trial met its primary end-point of confirming non-inferiority of gefitinib compared with docetaxel for OS. Thus docetaxel, erlotinib, gefitinib and pemetrexed are recommended as 'standard' choices for second-line therapy of NSCLC.

Conclusion

The addition of bevacizumab to chemotherapy doublets and the use of gefitinib and erlotinib has improved the outcome in selected patients with advanced NSCLC. Hopefully, advances in understanding the molecular biology of cancer and mechanisms of tumourigenesis will facilitate the discovery and development of novel 'targeted agents' and will further improve outcomes for these patients. ■

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