Second- and Third-line Treatment in Advanced Non-small-cell Lung Cancer

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Abstract

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. About 50% of patients present with locally advanced or metastatic disease. First-line therapy usually consists of a combination of cisplatin or carboplatin with a third-generation agent (paclitaxel, docetaxel, gemcitabine or vinorelbine) that results in less than 5% five-year survival. In recent years advances in second- and third-line treatment have led to a prognostic improvement. Two cytotoxic agents, docetaxel and pemetrexed, are approved in NSCLC second-line treatment, and a new class of drugs against specific molecular targets – tyrosine kinase inhibitors – has emerged as an alternative to conventional treatment. Many trials are ongoing to assess the activity of new drugs, alone or in association, or new combinations of third-generation chemotherapeutic agents.

Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases. About 50% patients present with locally advanced or metastatic disease, and their five-year survival amounts to less than 5%.[1] First-line chemotherapy in advanced NSCLC usually consists of a combination of cisplatin or carboplatin with a third-generation agent (paclitaxel, docetaxel, gemcitabine or vinorelbine). About 30% of patients treated in first-line with one of these combinations achieve a response lasting for four to five months. For a long period the results of second-line treatment of advanced NSCLC were disappointing in terms of both response rate and survival.

Single-agent Chemotherapy

Docetaxel (Taxotere®, sanofi-aventis) as second-line treatment was the first drug to show in phase III trials an advantage in survival and quality of life (QoL) compared with best supportive care (BSC) (TAX 317)[2] and with single-agent treatment with ifosfamide (Ifex®, Bristol-Myers Squibb Co.) or vinorelbine (Navelbine®, Pierre Fabre Pharmaceuticals) (TAX 320).[3] The better toxicity profile with the weekly compared with the three-weekly schedule was shown in the TAX 320 trial and confirmed in many randomised clinical trials and two meta-analyses,[4,5] with no significant differences in survival. Recently, the multitarget antifolate agent pemetrexed (Alimta®, Eli Lilly and Co.) demonstrated a similar clinical response to and a better safety profile than docetaxel in second-line treatment of NSCLC patients. Both agents provided a median survival of about eight months, one-year survival of 30% and a response rate of 10%, with less haematological toxicity in the pemetrexed arm.[6] Due to its good toxicity profile, even elderly and performance status (PS) 3 patients, for whom the American Society of Clinical Oncology (ASCO) guidelines contraindicate any chemotherapy, could benefit from pemetrexed.[7,8]

Histology is an important factor in treatment selection in both first- and second-line treatment with pemetrexed, due to the different expression of thymidylate synthase (TS) between adenocarcinoma and squamous cell carcinoma. A retrospective analysis of the data of the pemetrexed versus docetaxel phase III study indicated that the squamous cell subgroup patients treated with docetaxel had statistically better survival than patients treated with pemetrexed. Conversely, in the non-squamous subgroup pemetrexed was statistically superior to docetaxel.[9] Among third-generation cytotoxic agents, gemcitabine (Gemzar®, Eli Lilly and Co.) and paclitaxel showed promising activity and acceptable toxicity profile as single agents in the second-line treatment of advanced NSCLC.[10,11] Some patients seem to benefit more than others from second-line treatment with paclitaxel (e.g. patients with stable disease after a first-line platinum-based therapy, or a longer time to relapse). Table 1 shows some meaningful phase III trials performed in recent years.

Combination Chemotherapy

Several phase II trials showed that combination regimens induced similar survival to and higher toxicity than single-agent chemotherapy; nevertheless, some combinations achieved encouraging results. Irinotecan in association with different agents was tested in some phase II trials. A total of 373 patients were treated, achieving a median response rate of 14% (9–26%) and a median survival of eight months (seven to 11 months). Gemcitabine combined with taxanes was administered to a total of 92 patients, showing a response rate of about 30% and overall survival of about nine months. A phase III randomised trial comparing pemetrexed plus carboplatin with pemetrexed alone in pre-treated NSCLC patients was recently performed. This trial showed a significant improvement of

Table 1: Main Phase III Randomised Trials in Pre-treated Non-small-cell Lung Cancer Patients

Second-line Regimen	Number of Patients	RR (%)	MST (months)	One-year Survival (%)	TTP (months)	Author/Reference
Docetaxel (75) versus placebo	55 versus 100	6 versus NE	7.5 versus 4.6	37 versus 11	2.5 versus 1.5	Shepherd et al.[2]
Docetaxel versus ifosfamide/vinorelbine	125 versus 89/34	7 versus <1	5.7 versus 5.5	32 versus 19	2 versus 2	Fossella et al.[3]
Docetaxel versus pemetrexed	288 versus 283	9 versus 9	7.9 versus 8.3	30 versus 30	3.5 versus 3.4	Hanna et al.[6]
Erlotinib versus placebo	488 versus 243	9 versus <1	6.7 versus 4.7	31 versus 22	2.2 versus 1.8	Shepherd et al.[15]
Gefitinib versus placebo	1,129 versus 563	8 versus 1	5.6 versus 5.1	27 versus 21	3 versus 2.6	Thatcher et al.[14]
Gefitinib versus docetaxel	733 versus 733	NR	7.6 versus 8.0	32 versus 34	2.2 versus 2.7	Kim et al.[17]
Vinflunine versus docetaxel	272 versus 275	4.4 versus 5.5	6.7 versus 7.2	NR	2.3 versus 2.3	Douillard et al.[36]
Oral topotecan versus docetaxel IV	414 versus 415	5 versus 5	7 versus 7.8	25 versus 29	2.8 versus 3	Ramlau et al.[37]

RR = response rate; MST = median survival time; TTP = time to progression; NE = not evaluable; NR = not reported.

progression-free survival (PFS) in the group of patients treated with the combination regimen.[12] So far, no phase III trial has shown an improvement of survival when a doublet regimen was compared with single-agent chemotherapy, and a recent meta-analysis of four phase II and two phase III trials confirmed that second-line doublet chemotherapy is more toxic and does not improve overall survival, even if PFS and response rate have significantly improved.[13]

Targeted Therapies

The development of biologic agents active against specific molecular targets represents an innovation of antitumour research. Epidermal growth factor receptor (EGFR) is expressed in most NSCLCs and its tyrosine kinase intra-cytoplasmic subunit is the molecular target of a new class of agents, tyrosine kinase inhibitors (TKIs), recently introduced in NSCLC treatment. Most randomised trials are focused on gefitinib (Iressa®) and erlotinib (Tarceva®). Gefitinib, approved in 2003 by the US Food and Drug Administration (FDA) for the third-line treatment of NSCLC, and since 2005 limited to patients included in clinical trials, was then retired because a phase III randomised trial demonstrated no survival advantage compared with placebo when administered at a dose of 250mg/day in pre-treated patients. Survival time favouring gefitinib was very different in the two treatment groups for non-smokers and Asian patients.[14] The BR.21 trial[15] showed a better overall survival and 9% response in the erlotinib group. Based on these data, the FDA in 2004 and the European Medicines Agency (EMEA) in 2005 approved erlotinib for the treatment of patients in a second- or third-line setting. Although response to erlotinib was more frequent in women with adenocarcinoma, never-smokers or East Asians, an exploratory analysis of the BR.21 study showed smoking status as the most powerful predictor of a survival effect; similar results were seen in the Iressa Survival Evaluation in Lung cancer (ISEL) trial. Gefitinib and erlotinib are thought to have a similar mechanism of action but different outcomes in these two large phase III studies, even if there were no striking differences in response rate and survival benefit. One explanation could be that gefitinib was underdosed, but a higher dose of gefitinib has not been shown to be more effective. Another possibility was that the ISEL study had a different population with highly refractory disease, absent in the BR.21 study, even though the inclusion criteria in the latter trial required patients to be unfit for further chemotherapy.

Besides clinical features such as smoking status, gender and race, at least two potential biomarkers – EGFR mutations and EGFR amplifications – have been identified by translational research. Mutations of exons 19 and 21 have been associated with remarkable responses to TKIs, and these mutations are more frequent in never-smokers, women, patients of Asian origin or those with a history of adenocarcinoma or bronchioloalveolar carcinoma. Patients carrying those mutations had no survival advantage but higher objective responses, although not statistically significant. EGFR immuno-histochemical expression was not significantly related to response in former phase II trials, while in the BR.21 study EGFR expression was associated with response to erlotinib but not with survival.[16] EGFR expression is commonly associated with amplification or high polysomy of the EGFR gene. In the above-mentioned BR.21 trial, the EGFR gene copy number assessed by fluorescence *in situ* hybridisation (FISH) seemed to be the most important predictive factor of response and survival, even if the recently performed Iressa Non-small-cell lung cancer Trial Evaluating REsponse and Survival against Taxotere (INTEREST) trial[17] raised some doubts: is it a prognostic and not a predictive factor? A score system has been detailed to stratify patients for TKI therapy on the basis of molecular features.[18] Some molecular mechanisms involved in primary or acquired TKI resistance have been identified. A secondary resistance EGFR mutation is often acquired in exon 20, T790M, and occurs in 50% of patients relapsed after an initial response. KRAS mutations may be considered the main mechanism involved in primary resistance, and usually occur in smoker patients or in absence of EGFR mutations. Hepatocyte growth factor (HGF) receptor (MET) amplification is responsible for TKI acquired resistance in 20% of NSCLC, but its role in primary refractivity among a cohort of patients with clinical and biological response predictors has not been confirmed.[19]

The use of monoclonal antibodies such as cetuximab (Erbitux®, Bristol-Myers Squibb Co.), acting against the extracellular subunit of EGFR, represents an alternative way to target this pathway. Cetuximab shows promising antitumour activity in the first- or second-line treatment of NSCLC, both in association with cytotoxic agents and as a single agent.[20,21] Targeted therapy development led to many trials dealing with the association of agents targeting the molecular pathways involved in tumour progression. Bevacizumab (Avastin®, Genentech Inc.) is a monoclonal antibody targeting vascular endothelial growth factor (VEGF), involved in angiogenesis. The association of erlotinib and bevacizumab seems to be a promising option in the treatment of relapsed NSCLC after at least one line of chemotherapy, possibly with the addition of a cytotoxic agent.[22,23] A single-centre retrospective analysis showed no difference in overall survival, time to progression and response rate between pemetrexed with or without bevacizumab, so a trial to assess whether bevacizumab improves the efficacy of

pemetrexed was planned.[24] A new class of multitargeted TKIs has emerged in recent years and has been studied in the NSCLC second-line setting. Sunitinib (Sutent®, Pfizer Inc.) is an oral TKI acting against VEGFR, PDGFR, KIT, RET and FLT3, approved for the treatment of renal cancer and imatinib-resistant gastrointestinal stromal tumour (GIST). Recent phase II trials have shown that sunitinib has promising single-agent activity in patients with recurrent NSCLC, with an objective response rate (ORR) similar to that of currently approved agents and an acceptable safety profile. Further evaluation in combination with other targeted agents and chemotherapy in patients with NSCLC is warranted.[25,26] Sorafenib (Nexavar®, Bayer Healthcare Pharmaceuticals) is an oral multikinase inhibitor that targets the Raf/MEK/ERK pathway at the level of Raf kinase and receptor tyrosine kinases. It has been studied in phase II trials, showing promising efficacy in patients with advanced, progressive NSCLC.[27,28] Vandetanib (Zactima®, AstraZeneca Pharmaceuticals) is an antitumour agent targeting VEGFR-dependent angiogenesis and the cell growth and survival mediated by EGFR and RET. The promising results obtained in phase II led to phase III trials evaluating this agent versus placebo in patients pre-treated with EGFR inhibitors, versus erlotinib and in association with docetaxel or pemetrexed.[29] Compared with single-agent docetaxel, vandetanib 100mg/day plus docetaxel showed a significant prolongation of PFS,[30] and these promising results led to a phase III trial.

New Chemotherapeutic Agents

New chemotherapeutic drugs are needed to overcome the intrinsic or acquired resistance limiting the efficacy of the most common antitumour agents. Epothilones A and B (patupilones) and their synthetic analogues (ixabepilone, epothilone B, ZK-EPO, BMS-310705 and KOS-1584) represent a new class of tubulin-stabilising agents, functionally and structurally different from taxanes, which induce the arrest of cell cycle and subsequently cell apoptosis. Although epothilones are active in taxane-resistant pre-clinical models, it is not clear whether their activity is higher than that of docetaxel or paclitaxel or whether they have a different toxicity profile.[31–34]

Lipoplatin is a new platinum analogue providing partial responses in 5% and stable diseases in 16% of patients, with a median survival of seven months.[35] Its toxicity profile led to a dosage increase in further phase I–II trials. Compared with docetaxel, vinflunine – a new vinca alkaloid[36] – and oral topotecan may be options for second-line treatment of NSCLC patients.[37] SNS-595 is a cell-cycle inhibitor that damages the DNA, blocks the cell cycle in G2 phase and induces apoptosis. The dosage of 48mg/m^2 is an active dose in the treatment of NSCLC with stable disease in more than 50% of patients.[38]

Conclusions

Advanced NSCLC still has a bad prognosis, with a median survival of about 12 months, which is nonetheless an improvement compared with the six-month survival reported about 20 years ago. The prognostic improvement in recent years is clearly associated not only with the optimisation of first-line treatment but also with the development of second- and third-line therapies. Docetaxel (administered weekly or every three weeks) and pemetrexed are the two agents now commonly used as second-line treatment of NSCLC in clinical practice. To date, combination chemotherapy has shown no advantage compared with single agents. Several trials are ongoing to assess the efficacy of combinations among chemotherapy and target drugs. Erlotinib 150mg/day is now used as third-line treatment of NSCLC, in the second line mainly when chemotherapy is contraindicated or in patients selected by clinical or biomolecular findings. ■

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