The Two Revolutions in the Treatment of Advanced Non-small Cell Lung Cancer

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Abstract

In parallel with the evolution of therapeutic paradigms for advanced cancers, treatment of advanced non-small cell lung cancer (NSCLC) has been through the revolution of personalised medicine benefiting for a minority of patients whose disease depends on a single oncogenic genetic alteration targetable by specific tyrosine kinase inhibitors. As well as for some other tumour types, targeting immune checkpoints inhibitors has shown encouraging activity for some patients, suggesting the dawn of a second therapeutic revolution for a significant proportion of lung cancer patients.

Keywords

Non-small cell lung cancer, chemotherapy, targeted therapy, immunotherapy

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Changes that have been occurring since approximately 10 years in the treatment of advanced non-small cell lung cancer (NSCLC) constitute a good illustration of the evolving paradigms in oncology. Ten years ago, advanced NSCLC was considered as a single entity, resulting from tumour cells proliferation and was therefore treated with cytotoxic drugs. With this approach, it has been possible to obtain a small but significant prolongation of survival in first-line of treatment with platinum-based chemotherapy,[1] in second-line with docetaxel,[2] both compared to best supportive care and in second or third-line therapy with erlotinib in unselected patients compared to placebo.[3] Even if it was possible to give several successive lines of treatment including now maintenance chemotherapy in a significant proportion of NSCLC patients, improvement of survival was limited and median survival consistently remained below one year.[4] Clearly, other approaches seemed necessary to cross this one-year bar for median survival, all the more since this survival advantage might be also linked to stage migration due to improvement in staging techniques, increase in patients' selection for clinical trials and optimisation of supportive care.[5]

A first step for treatment personalisation came from taking histology into consideration for first and second-line treatment of advanced NSCLC. This resulted from the development of two drugs, first pemetrexed demonstrating activity only in non-squamous carcinoma[6] and second, bevacizumab with the evidence of crippling toxicity in squamous cell carcinoma.[7] However, the true first revolution was due to the discovery of mutations in the gene encoding for epidermal growth factor receptor (EGFR), even there in relation to a drug development by sequencing EGFR in patients responding to gefitinib.[8] This was the first demonstration that lung adenocarcinoma could result from one single genetic alteration, leading to an "oncogenic addiction" for tumour cells, which proliferation and survival depend on this genetically altered pathway. The Iressa Pan-Asia Study (IPASS) trial comparing gefitinib to chemotherapy in never-smoker Asian patients[9] was therefore a landmark trial showing that genetic criteria were superior to clinical characteristics for selecting the adequate treatment for these patients and that gefitinib provided a progression-free survival advantage over chemotherapy only in patients with EGFR activating mutations. Moreover, the improvement of survival for patients with EGFR mutations treated with EGFR tyrosine kinase inhibitors with a median survival of more than 30 months in some trials, indirectly proves that targeting the oncogenic signalling pathway undeniably changes the natural history of the disease.[10] Besides EGFR mutations, other oncogenic single genetic alterations have been identified, the first of which being the anaplastic lymphoma kinase (ALK) gene rearrangements that led to a rapid development of crizotinib as ALK inhibitor with a clear improvement of patients survival.[11] It is now possible to individualise some oncogenic genetic alterations in non-squamous carcinoma (EGFR, v-Raf murine sarcoma viral oncogene homolog B [BRAF], human epidermal growth factor receptor-2 [HER2], mesenchymal-epithelial transition [MET] or V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog [KRAS] mutations, ALK, c-ros oncogene 1 [ROS1], rearranged during transfection [RET], neurotrophic tyrosine receptor kinase [NTRK] rearrangements) with available corresponding specific targeted therapies (except for KRAS mutations) able to provide good and durable response.[12] Therefore, NSCLC should be considered as a group of distinct diseases on the basis of genome analysis rather as a single entity.

Nevertheless, two main limitations rapidly emerged with this paradigm of targeting a single genetic alteration in lung cancer. First, genetic alterations leading to a true oncogenic addiction ("driver" mutations), concern only a minority of patients with non-squamous lung carcinoma, who are mainly light or never smokers.[12] Furthermore, data coming from extensive genome sequencing of lung cancers tend to show that the main oncogenic alterations have already been identified even if the role of some rare rearrangements or epigenetic alterations likely remain to be discovered.[13] It is unlikely that targeting a single altered pathway in lung cancers without evidence for a driver mutation will lead to a relevant clinical effect due to the multiplicity of genetic alterations and redundancy in signalling pathways, especially in smokers. Second, emergence of acquired resistance inevitably occurs with the continuous therapeutic pressure put on the oncogenic pathway with a gradually increasing involvement of central nervous system. Even with the development of new generation inhibitors specifically designed to address the mechanisms of resistance,[14,15] tumour heterogeneity gradually increases with emergence of different sub-clonal resistance phenotypes leading to loss of targeted treatment efficacy and to the need for cytotoxic or combined therapies.

Both limitations might be addressed by targeting not only the tumour cells but also the tumour microenvironment. The use of anti-angiogenic agents was a first step in targeting interactions existing between tumour cells and their microenvironment, but the benefits obtained with agents targeting vascular endothelial growth factor pathway in advanced non-squamous lung carcinoma remained of a limited magnitude and of a transient duration with the major issue of the lack of predictive biomarkers.[16,17] The evidence that targeting cancer cells immune tolerance with immune checkpoint inhibitors against program death receptor 1 (PD1) or its ligand (PD-L1) could achieve durable responses in almost 20% of unselected pre-treated NSCLC patients, irrespective of histology, clearly change the perspective for lung cancer treatment with the unspoken hope of cure for metastatic disease.[18,19] Anti-PD1 or PD-L1 monoclonal antibodies will probably move soon to frontline therapy, likely either as single-agent for tumours with a high level of PD-L1 expression or in combination with other checkpoint inhibitors or chemotherapy, leading to a profound modification of treatment algorithms. Today, approximately 15–20% of Caucasian lung cancer patients have disease depending on an identifiable oncogenic pathway and are treated with specific tyrosine kinase inhibitors in first and second-line of treatment. Fifteen to twenty per cent of the remaining patients will already see their disease durably controlled with checkpoint inhibitors, with an expected increase of this proportion of patients benefiting from immunotherapy with combined treatments and predictive biomarkers.

Thus, and unexpectedly at the beginning of the 21st century, NSCLC is one of the solid tumour type that best reflects the change in the paradigms of advanced cancer treatment with the era of personalised medicine and more recently at the dawn of a second therapeutic revolution with the expected tidal wave of immunotherapy, assuming that healthcare systems will be able to deal with the increased of treatments costs. ■

1. Non-small Cell Lung Cancer Collaborative Group, Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials, *BMJ*, 1995;311:899–909.
2. Shepherd FA, Dancey J, Ramlau R, et al., Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy, *J Clin Oncol*, 2000;18:2095–103.
3. Shepherd FA, Pereira J, Ciuleanu T, et al., Erlotinib in previously treated non-small-cell lung cancer, *N Engl J Med*, 2005;353123–32.
4. Schiller JH, Harrington D, Belani CP, et al., Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer, *N Engl J Med*, 2002;346:92–8.
5. Noonan KL, Ho C, Laskin J, Murray N, The influence of the evolution of first-line chemotherapy on steadily improving survival in advanced non-small-cell lung cancer clinical trials, *J Thorac Oncol*, 2015;10:1523–31.
6. Scagliotti G, Parikh P, von Pawel J, et al., Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer, *J Clin Oncol*, 2008;26:3543–51.
7. Johnson DH, Fehrenbacher L, Novotny WF, et al., Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer, *J Clin Oncol*, 2004;22:2184–91.
8. Lynch TJ, Bell DW, Sordella R, et al., Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib, *N Engl J Med*, 2004;350:2129–39.
9. Mok TS, Wu YL, Thongprasert S, et al., Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma, *N Engl J Med*, 2009;361:954–7.
10. Yang JC, Wu YL, Schuler M, et al., Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials, *Lancet Oncol*, 2015;16:141–51.
11. Solomon BJ, Mok T, Kim DW, et al., PROFILE 1014 Investigators. First-line crizotinib versus chemotherapy in ALK-positive lung cancer, *N Engl J Med*, 2014;371:2167–77.
12. Barlesi F, Mazieres J, Merlio JP, et al., Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT), *Lancet*, 2016[Epub ahead of print].
13. Cancer Genome Atlas Research Network, Comprehensive molecular profiling of lung adenocarcinoma, *Nature*, 2014;511:543–50.
14. Shaw AT, Kim DW, Mehra R, et al., Ceritinib in ALK-rearranged non-small-cell lung cancer, *N Engl J Med*, 2014;370:1189–97.
15. Jänne PA, Yang JC, Kim DW, et al., AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer, *N Engl J Med*, 2015;372:1689–99.
16. Soria JC, Mauguen A, Reck M, et al., Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer, *Ann Oncol*, 2013;24:20–30.
17. Garon EB, Ciuleanu TE, Arrieta O, et al., Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial, *Lancet*, 2014;384:665–73.
18. Brahmer J, Reckamp KL, Baas P, et al., Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer, *N Engl J Med*, 2015;373:123–35.
19. Borghaei H, Paz-Ares L, Horn L, et al., Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer, *N Engl J Med*, 2015;373:1627–39.