Second line in NSCLC: new opportunities?

“...further advancements are needed to convert lung cancer into a chronic disease.”

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Every patient affected by advanced and recurrent NSCLC, despite modest outcome benefits from first-line therapy, experiences disease progression and requires salvage therapy. In second-line settings, only a small percentage of patients, in other words, those with oncogene-addicted NSCLC, can benefit from specific inhibitors if still not received at first line, and another small percentage may be enrolled in clinical trials. However, most ‘real-life population’ patients are molecularly unselected or ineligible for clinical trials and receive standard second-line therapy. We will discuss specifically this large group of patients.

Since 2000, when two randomized trials demonstrated that docetaxel improved overall survival (OS), symptom control and quality of life (QoL) compared with best supportive care and with vinorelbine or ifosfamide, the second-line approach became a standard of care [1,2]. It was the first scientific evidence that a salvage therapy worked, and this was considered another step forward in the fight against NSCLC, despite docetaxel showed more neutropenia and febrile neutropenia

compared with the control arm. A Phase III noninferiority trial showed pemetrexed was equally effective but with a better safety profile than docetaxel. Pemetrexed, reporting a better OS in nonsquamous carcinoma, is now available in clinical practice only for this NSCLC histotype [3]. Erlotinib, an orally available EGF receptor-tyrosine kinase inhibitor (EGFR-TKI), improved OS and QoL compared with placebo in second- and third-line treatment of unselected NSCLC patients [4]. On the other hand, gefitinib, another EGFR-TKI, failed to improve OS compared with placebo, and was not approved in Western countries [5]. To date, docetaxel and pemetrexed, only in nonsquamous carcinoma histotype, and erlotinib are registered for second-line therapy, and erlotinib also for third-line treatment. It is estimated that only 30–50% of NSCLC patients are able to receive second-line therapy, with best supportive care the most frequent approach in this setting, being another important potential option to discuss with the patient. Unfortunately, for those receiving second-line treatment, clinical outcomes remain poor, with response rates lower than 10%

KEYWORDS

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and a median OS of 7–9 months from the start of second-line therapy [6].

In order to improve these results, two questions were addressed whose answers were: doublet chemotherapy does not improve OS compared with single-agent therapy and increases toxicity [7,8]; in unselected patients, EGFR-TKIs, gefitinib and erlotinib, show similar activity but different safety profiles compared with single-agent docetaxel or pemetrexed [9–11].

At this point, excluding patients with onco-gene-addicted NSCLC, we have two possible scenarios: patients whose tumors are *EGFR* wild-type, and those with unknown *EGFR* status. For the first scenario, two Phase III trials showed that docetaxel improved progression-free survival (PFS) over erlotinib [12,13] and only one trial showed improved OS [12]. A further Phase III trial showed that serum protein test status is predictive of differential benefits in OS for erlotinib versus chemotherapy, and patients classified as likely to have a poor outcome reported better results with chemotherapy [14]. However, disease responses to erlotinib were reported also in patients with *EGFR* wild-type NSCLC, underlining the different sensitivity and specificity of the available molecular testing and that mutation tests are biased by false-negative and probable false-positive results [12,13]. However, when a patient has a known *EGFR* wild-type NSCLC, chemotherapy should be the treatment of choice. In the second scenario, the unknown *EGFR* mutational status is mainly due to the lack of adequate amount of tissue to analyze. If further biopsy is not feasible, after discussing with the patient their ability and willingness to undergo the treatment, second-line chemotherapy is a reasonable choice, leaving erlotinib as third-line therapy. In patients ineligible for further chemotherapy, erlotinib could be a valid second-line option. However, we think that in both scenarios the choice of the best diagnostic and/or treatment approaches should be guided by the clinical characteristics of patients. Adenocarcinoma histotype, female, younger age, never-smoker and Asian ethnicity are factors related to a higher probability of *EGFR* mutations [15], requiring further tissue for molecular analyses. In this view, the analysis of plasma-derived circulating-free tumor DNA could help, because this is found in the blood, providing a noninvasive and thus less risky alternative method to repeated tumor biopsies and to monitor tumor progression. This procedure has already been registered

for detecting *EGFR* mutations when tumor tissue is not available, because high concordance, specificity and sensitivity were demonstrated within a Phase IV study investigating gefitinib as first-line therapy in NSCLC *EGFR* mutated patients [16]. Performance status, patient comorbidities, response and its duration and tolerance to first-line chemotherapy, safety profile of the second-line drug and patient preference should help in the choice of the second-line agent [17].

Most of patients with nonsquamous NSCLC received, as first-line therapy, bevacizumab-based platinum combinations and, mainly, a pemetrexed-platinum regimen followed by maintenance pemetrexed [18]. These findings make docetaxel and erlotinib the standard second-line treatment options with docetaxel to be used in combination with the investigational drug. Lately, the second-line approach has added two new options: nintedanib (formerly known as BIBF 1120), an oral triple angiokinase inhibitor of VEGF receptor (VEGFR)-1, -2 and -3, FGF receptor (FGFR)-1, -2 and -3 and PDGF receptor (PDGFR) α and β tyrosine kinases [19]; and ramucirumab, a fully human IgG1 monoclonal antibody that specifically binds to the VEGFR-2 extracellular domain with high affinity, preventing binding of all VEGF ligands and receptor activation [20]. In the Phase III LUME-Lung 1 trial, 1314 patients with advanced NSCLC progressing after first-line therapy were randomized to either docetaxel 75 mg/m² every 3 weeks plus nintedanib 200 mg twice daily or placebo. Nintedanib plus docetaxel significantly prolonged PFS with 3.4 versus 2.7 months, respectively (hazard ratio [HR]: 0.79; $p = 0.0019$). This improvement was reported regardless of histology with the same advantage in squamous (HR: 0.77; $p = 0.02$) and adenocarcinoma (HR: 0.77; $p = 0.02$) histotypes. OS was significantly prolonged in all adenocarcinoma patients with a median of 12.6 versus 10.3 months, respectively. Disease control rates were significantly improved in all patients (odds ratio [OR]: 1.68; $p < 0.0001$). The most common adverse events were diarrhea and alanine transaminase elevations. Withdrawals due to adverse events were similar in both arms [19]. The results of this study led to the registration of nintedanib in combination with docetaxel in second-line treatment of patients affected by lung adenocarcinoma. In the REVEL Phase III study, 1253 patients were randomized, as second-line therapy, to either

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docetaxel 75 mg/m² every 3 weeks plus ramucirumab 10 mg/kg every 3 weeks or matching placebo. OS, the primary endpoint, resulted significantly improved in the ramucirumab arm, reporting a median of 10.5 and 9.1 months, respectively (HR: 0.86; *p* = 0.023). Median PFS was 4.5 and 3.0 months, respectively (HR: 0.76; *p* < 0.0001). Disease control rates were 64% in the ramucirumab group and 53% in the control arm (OR: 1.60; *p* < 0.0001). The most common grade ≥3 adverse events were neutropenia (49% in the ramucirumab group vs 40% in the control group), febrile neutropenia (16 vs 10%) and hypertension (6 vs 2%). Toxic death and grade ≥3 pulmonary hemorrhage did not differ between groups. Notably, 25% of enrolled patients had squamous histotype and all ramucirumab outcomes, including OS advantage, were confirmed regardless of NSCLC histology [20]. This is the first evidence of efficacy of an antiangiogenic monoclonal antibody in squamous lung carcinoma without increasing the incidence of adverse events, especially bleeding or hemorrhage. Based on these results, ramucirumab was granted registration in combination with docetaxel in second-line therapy of any histology NSCLC.

Two more questions: is once every 3 weeks docetaxel the best companion for investigational agents? We know that weekly docetaxel showed similar OS and less hematologic toxicity [17]. Unfortunately, weekly schedule is frequently used in clinical practice but never in clinical trials. Should targeted therapy be used in unselected patients? Nintedanib and ramucirumab

were granted registration for the treatment of biologically unselected patients. We think that targeted therapy is to be preferred when a target is actually present for a ‘personalized medicine’ approach to optimize results. In this view, the registration of these new targeted agents looks like a step backwards, but we think that in the fight against lung cancer any news is good news. When a drug–target match is not available, clinical trials for unselected patients should be strongly considered whenever available. In this view, trials incorporating agents anticytotoxic T-lymphocyte antigen 4 or targeting programmed death (PD)-1 and PD-Ligand 1 performed regardless of any clinical and/or biological selection seem particularly promising.

Second-line endpoints in patients with NSCLC are improved OS, better QoL and low toxicity. When a molecular target is unavailable, the clinical selection of patients is mandatory to optimize the treatment currently available in this setting. Although much has already been done, further advancements are needed to convert lung cancer into a chronic disease.

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